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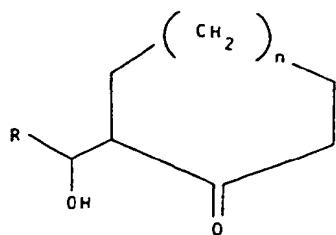
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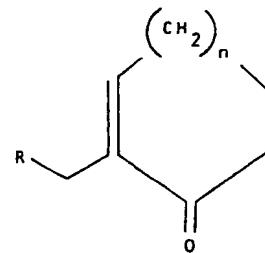
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(54) Process for the preparation of methyl dihydrojasmonate and homologues.

(57) There is provided a process of reacting a compound defined according to the structure:



with HX in the presence of n-butanol or toluene in order to form, in one step, a compound having the structure:



wherein n is 0 or 1, and wherein R is C<sub>1</sub>-C<sub>4</sub> alkyl and X is chloro or bromo.

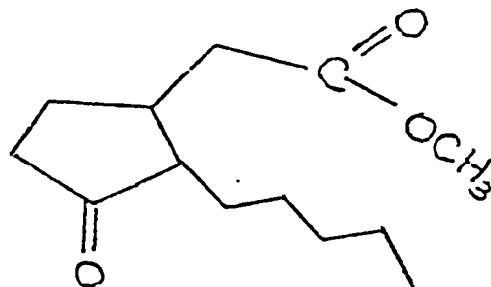
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Process for the preparation of methyl dihydrojasmonate and homologues

Methyl dihydrojasmonate having the structure:

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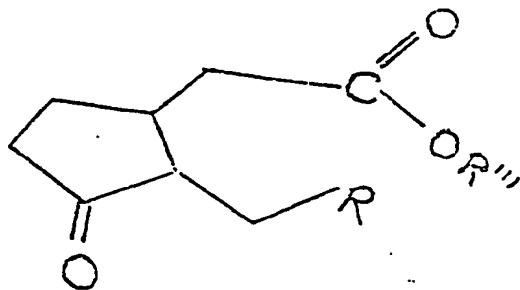


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and alkyl and alkylene homologues thereof defined according to the structures:

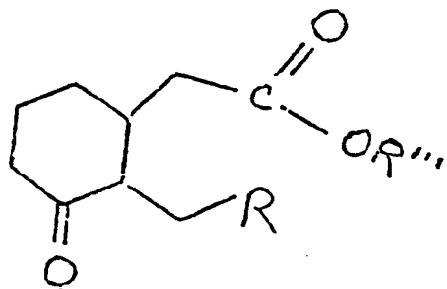
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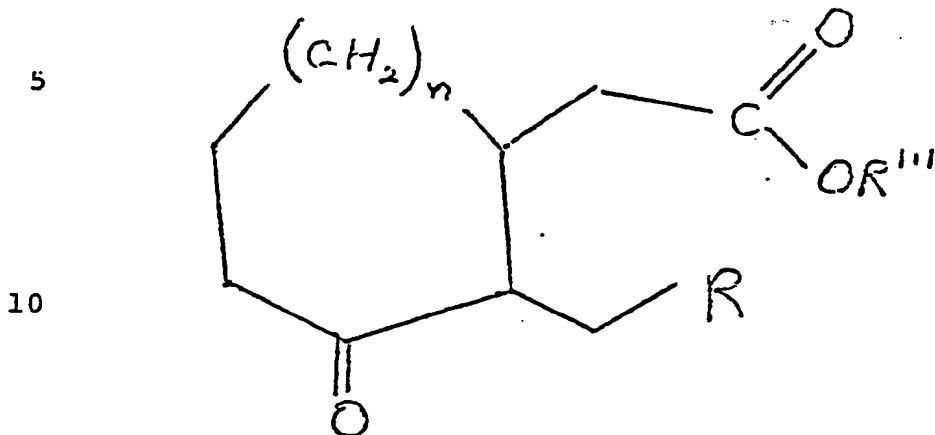
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or the generic structure:

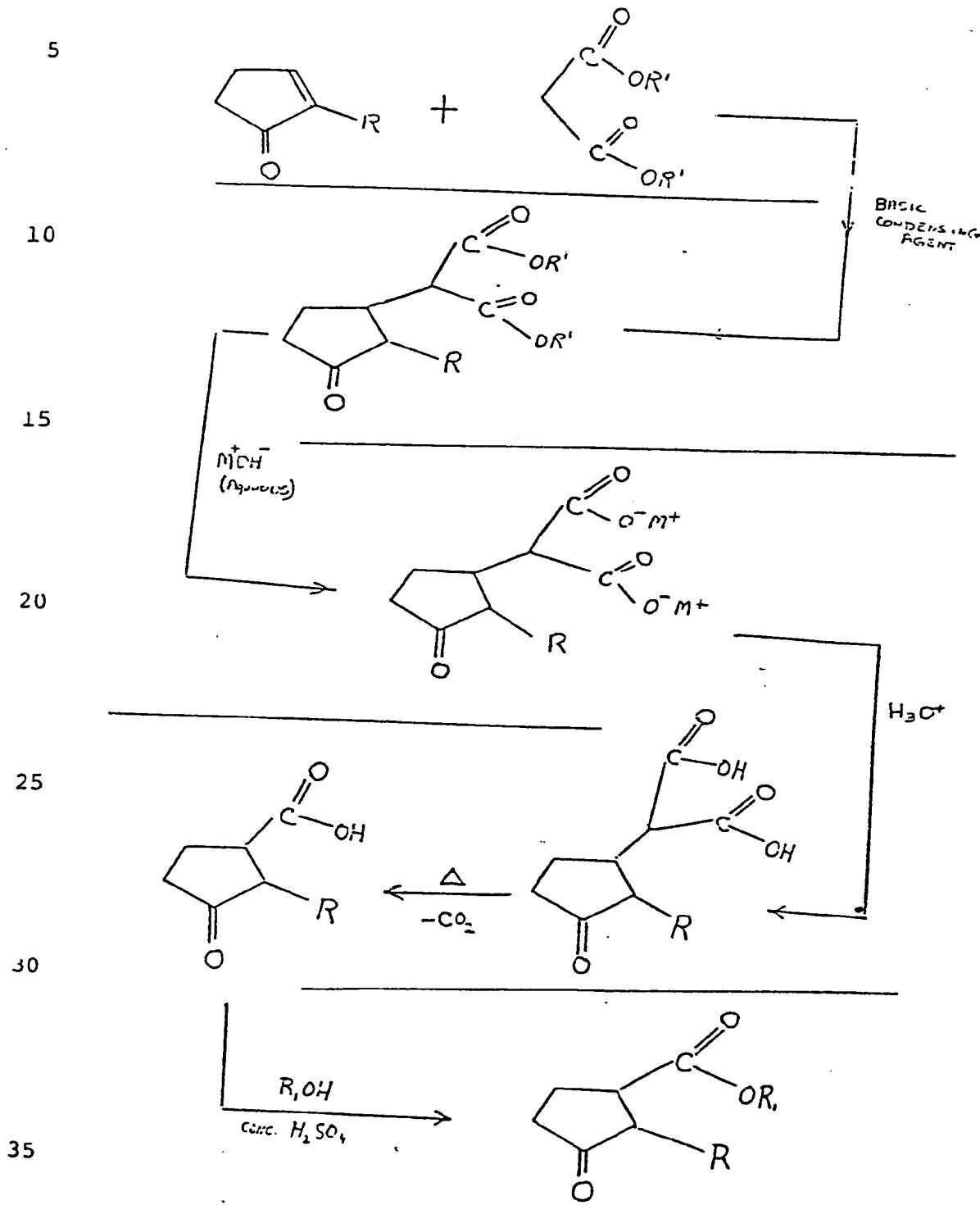


wherein n is 0 or 1 and wherein R is C<sub>1</sub>-C<sub>4</sub> alkyl and R''' represents C<sub>1</sub>-C<sub>3</sub> alkyl are valuable ingredients useful as medicinal drug intermediates and perfumery materials; for use in augmenting or enhancing the aroma of perfumes, 20 perfumed articles such as nonionic, anionic, cationic or zwitterionic detergents or dryer-added fabric softener articles or colognes.

Methyl dihydrojasmonate has been previously shown to be 25 prepared in United Kingdom Patent Specification 907,431 published on October 3, 1962, according to the process:

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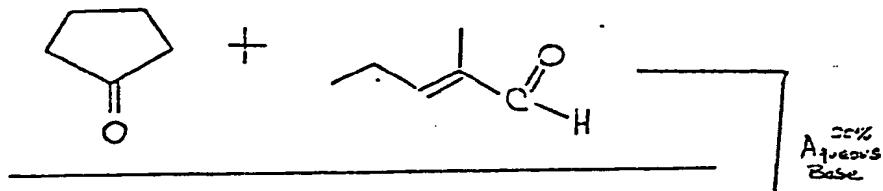
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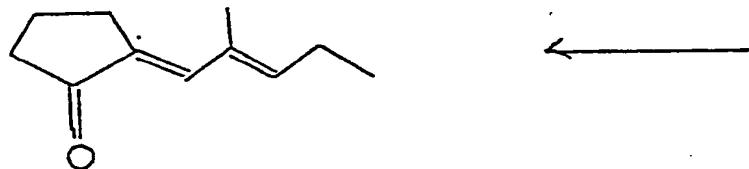
wherein R' is methyl or ethyl and R represents lower alkyl, and wherein R<sub>1</sub> represents lower alkyl and M represents alkali metal such as potassium or sodium.

5 Furthermore, the prior art sets forth alkylidenylation reactions with cyclopentanone and unsaturated aldehydes according to the reaction sequence:

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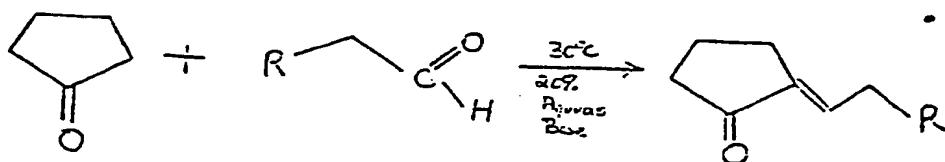


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(Vol. 78 Chemical Abstracts 59537k (abstract of Mekhtiev et al, Azerb. Khim. Zh. 1973 (1), 47-51)) and the reaction:

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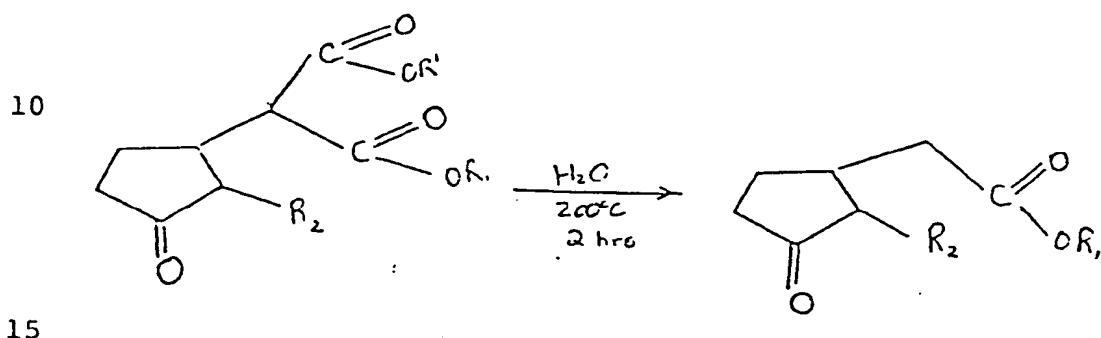
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(Vol. 79 Chemical Abstracts 78170t (abstract of Mekhtiev et al, Azerb. Khim. Zh. 1972 (4), 50-5)) wherein R is propyl or isopropyl.

5 German Offenlengungsschrift 27 32 107, published on January 9, 1978, sets forth the reaction:



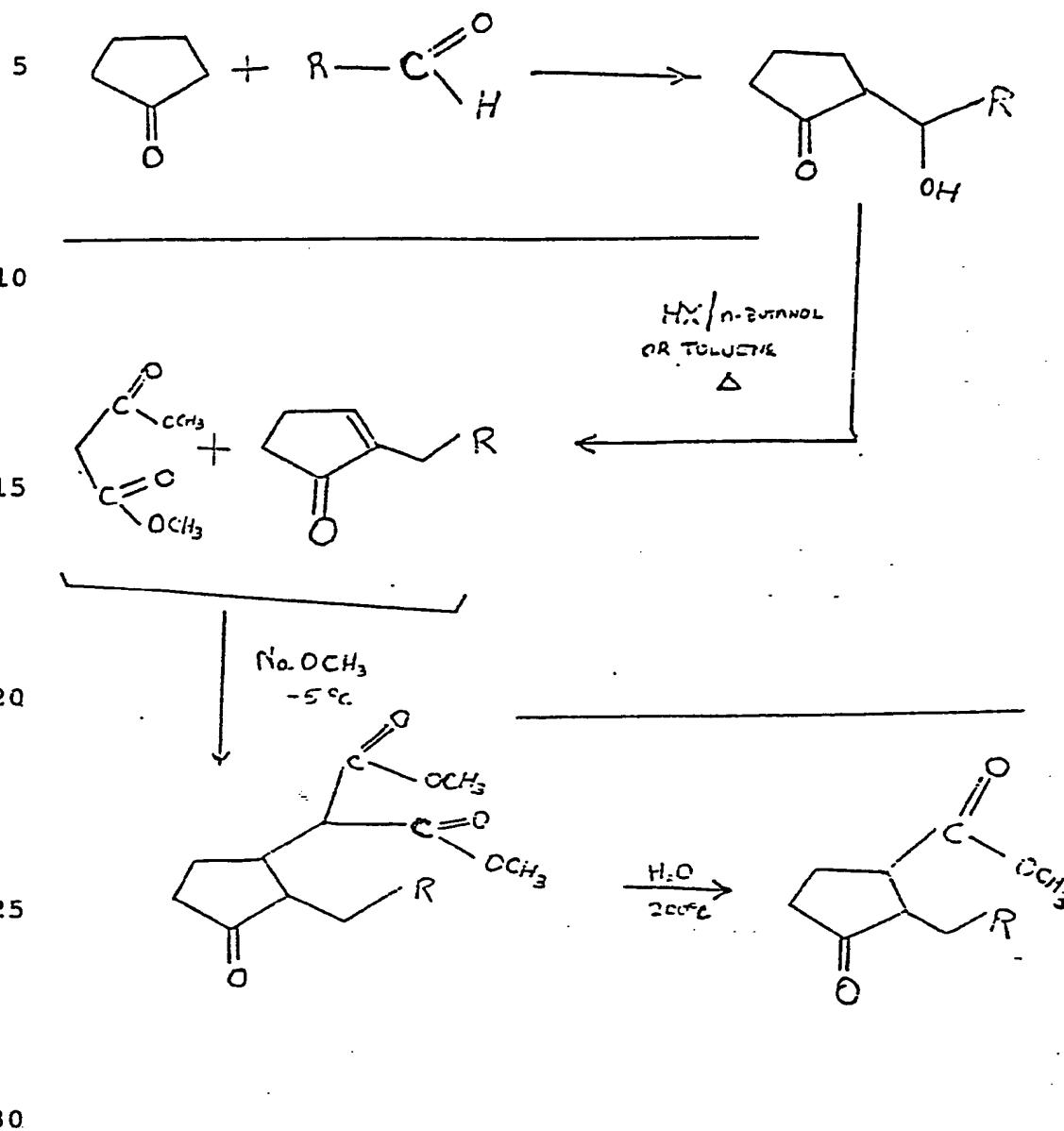
(abstracted in Chem. Abstract Vol. 88, 169667a).

Nothing in the prior art, however, indicates the highly efficient reaction sequence leading to methyl dihydrojasmonate or lower alkyl homologues thereof according to the reaction sequence:

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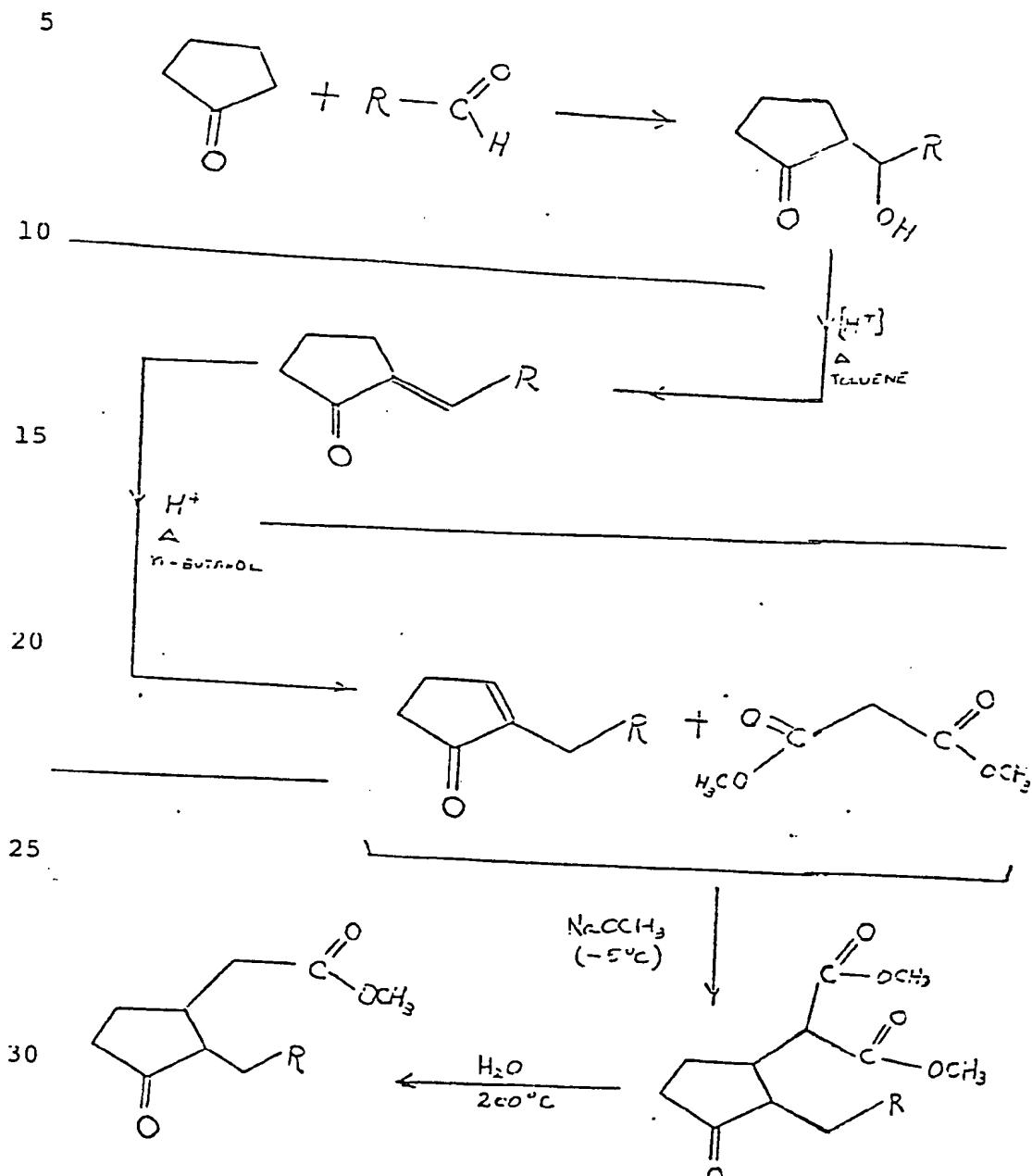
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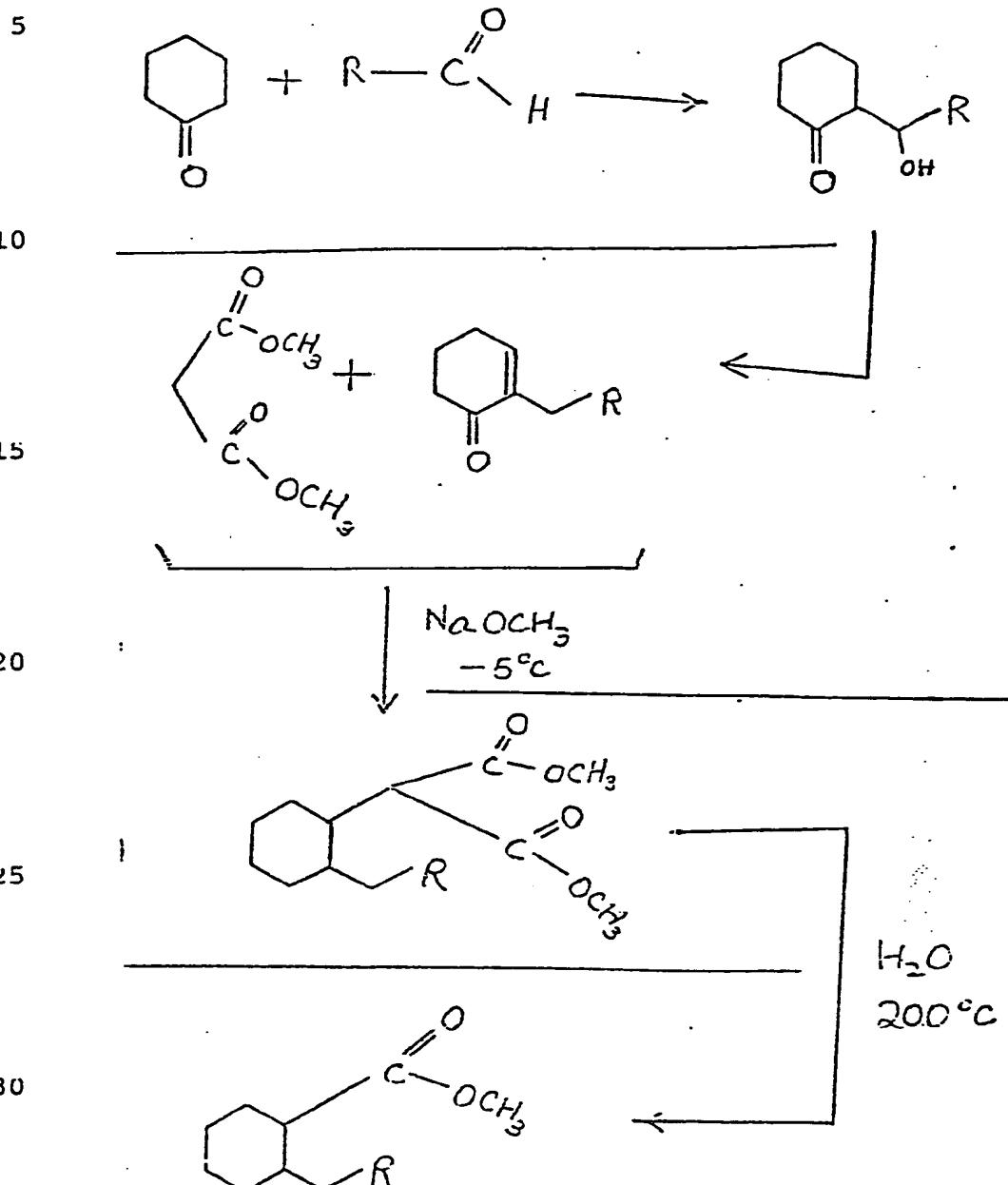
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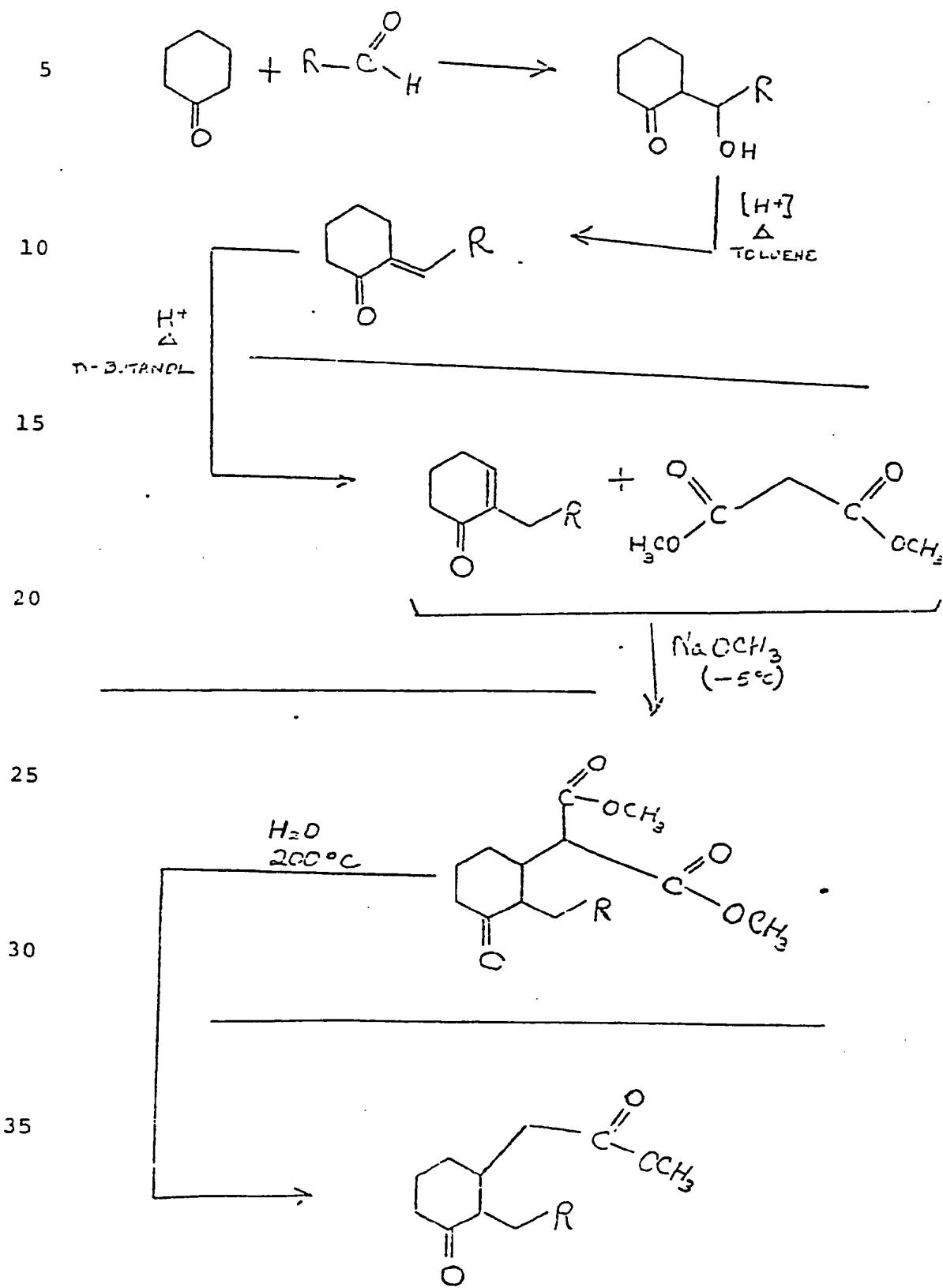
or the reaction sequence:



or the reaction:



or the reaction:



wherein R is C<sub>1</sub>-C<sub>4</sub> alkyl; X is chloro or bromo; and n is 0 or 1.

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Brief description of the drawings

Figure 1 represents the GLC profile for fraction 1 resulting from the fractional distillation of the reaction product produced according to Example I(D).

Figure 2 represents the GLC profile for fraction 2 resulting from the fractional distillation of the reaction product produced according to Example I(D).

10

Figure 3 represents the GLC profile for fraction 3 resulting from the fractional distillation of the reaction product produced according to Example I(D).

15 Figure 4 represents the GLC profile for fraction 4 resulting from the fractional distillation of the reaction product produced according to Example I(D).

Figure 5 represents the GLC profile for fraction 5 resulting from the fractional distillation of the reaction product produced according to Example I(D).

Figure 6 represents the GLC profile for fraction 6 resulting from the fractional distillation of the reaction product produced according to Example I(D).

Figure 7 represents the GLC profile for fraction 7 resulting from the fractional distillation of the reaction product produced according to Example I(D).

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Figure 8 represents the GLC profile for fraction 8 resulting from the fractional distillation of the reaction product produced according to Example I(D).

35 Figure 9 represents the GLC profile for fraction 9 resulting from the fractional distillation of the reaction product produced according to Example I(D).

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Figure 10 represents the GLC profile for figure 10 resulting from the fractional distillation of the reaction product produced according to Example I(D).

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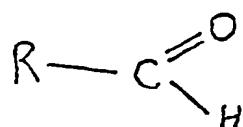
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The invention

The invention, accordingly, comprises the novel process and steps, specific embodiments of which are also described hereinafter by use of experiments and in accordance with what is now the preferred practice of the invention.

The process of our invention comprises reacting a C<sub>2</sub>-C<sub>5</sub> aldehyde having the structure:

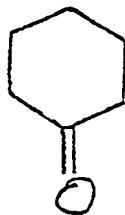
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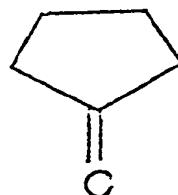
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with a cycloalkanone having the structure:

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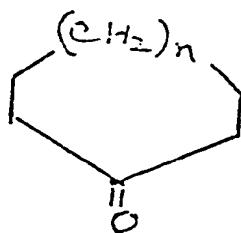
or



25

or defined according to the generic structure:

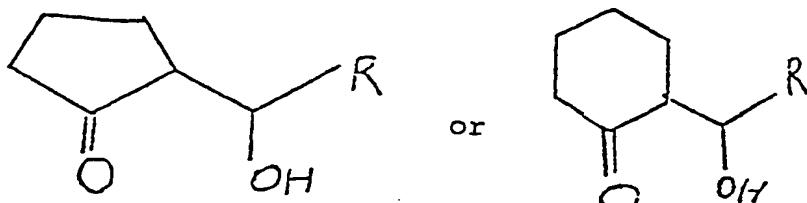
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wherein  $n$  is 0 or 1, to form an aldol having the structure:

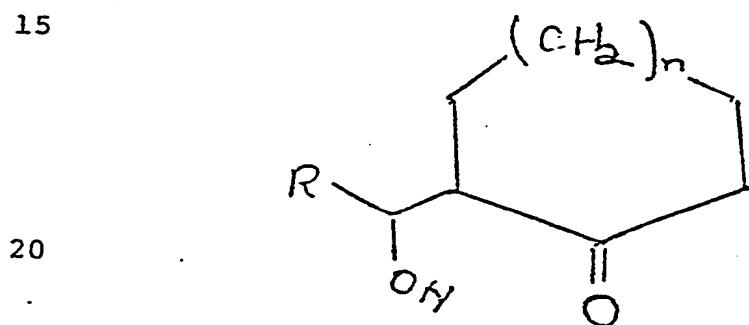
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or defined according to the generic structure:

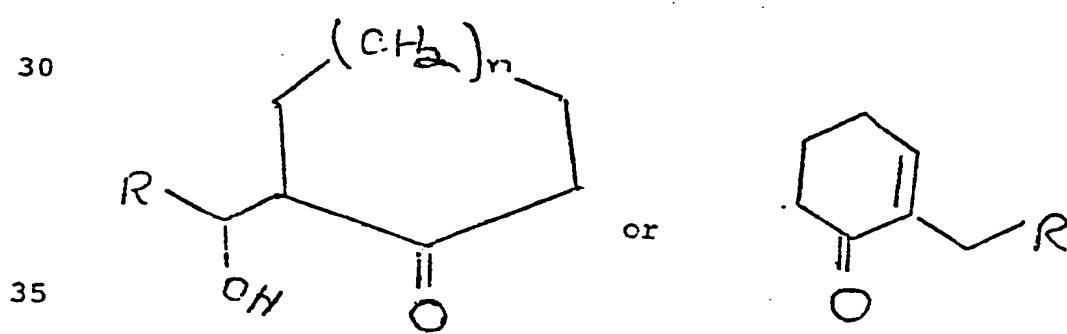
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wherein  $R$  is  $C_1-C_4$  alkyl and wherein  $n$  is 0 or 1, and then dehydrating the aldol to form the alkylidene cyclo-  
25 alkanone and then rearranging the thus-formed alkylidene cycloalkanone to form the alkyl cycloalkenone having the structure:

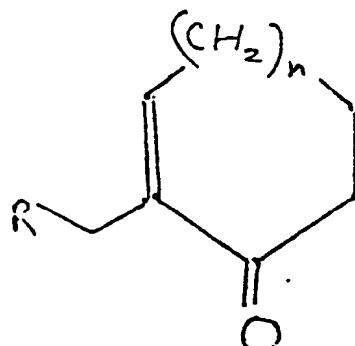
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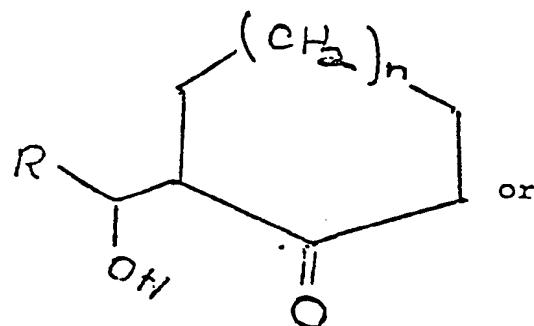
or defined according to the generic structure:

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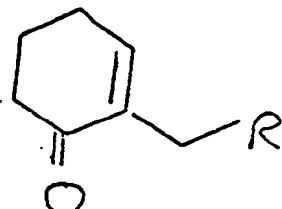


wherein R is C<sub>1</sub>-C<sub>4</sub> alkyl or n is 0 or 1; or, in the alternative, simultaneously dehydrating and rearranging the aldol to form the alkyl cyclopentenone having the  
15 structure:

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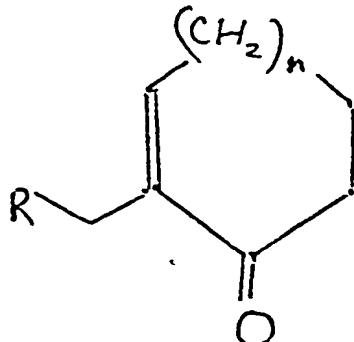


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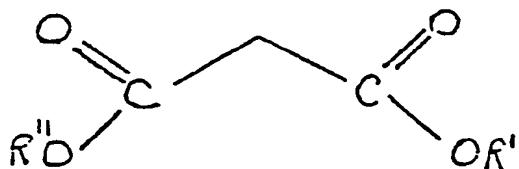
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wherein R and n are as defined above, then reacting the alkyl cyclopentenone with a malonic ester having the structure:

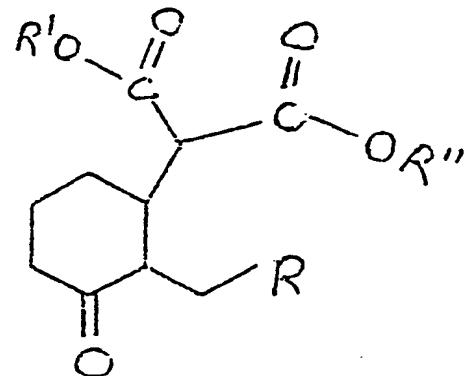
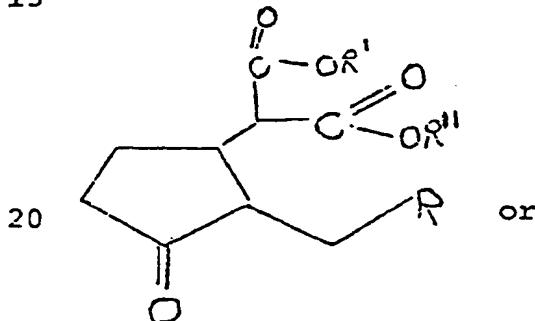
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thereby forming the malonic ester alkyl cycloalkanone reaction product having the structure:

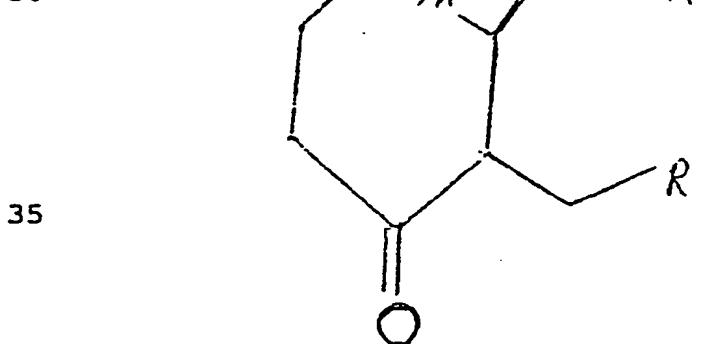
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or defined according to the generic structure:

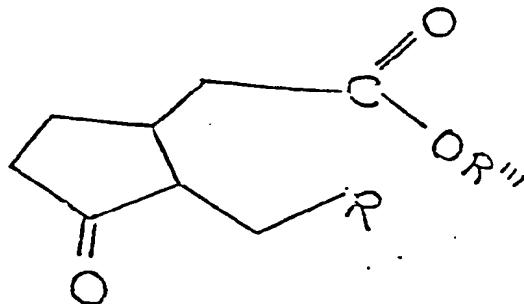
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then mono-decarboxylating the resulting malonic ester-alkyl cycloalkenone reaction product to form the methyl dihydrojasmonate or homologue thereof having the structure:

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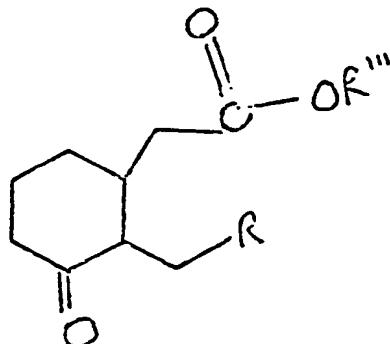
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or

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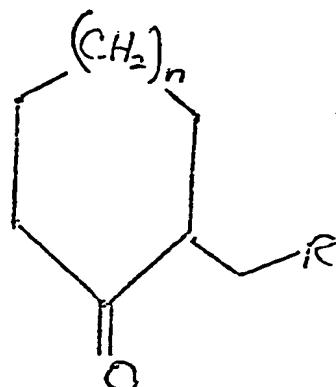


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or defined according to the generic structure:

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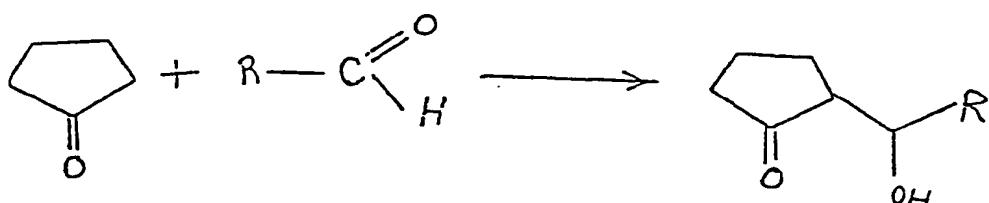


wherein n is 0 or 1 and wherein R is C<sub>1</sub>-C<sub>4</sub> alkyl; R' and R'' represent the same or different methyl or ethyl; R''' represents methyl or ethyl and X represents chloro or bromo.

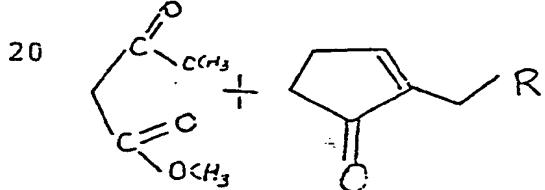
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In summary, the reaction of our invention may be represented in the alternative by one of the reaction schemes:

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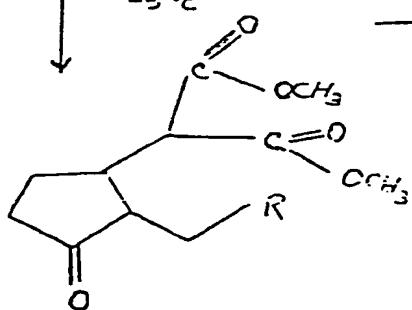
HX / n-BUTANOL  
OR TOLUENE  
Δ



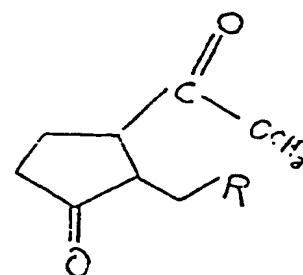
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NaOCH<sub>3</sub>  
-5°C

30

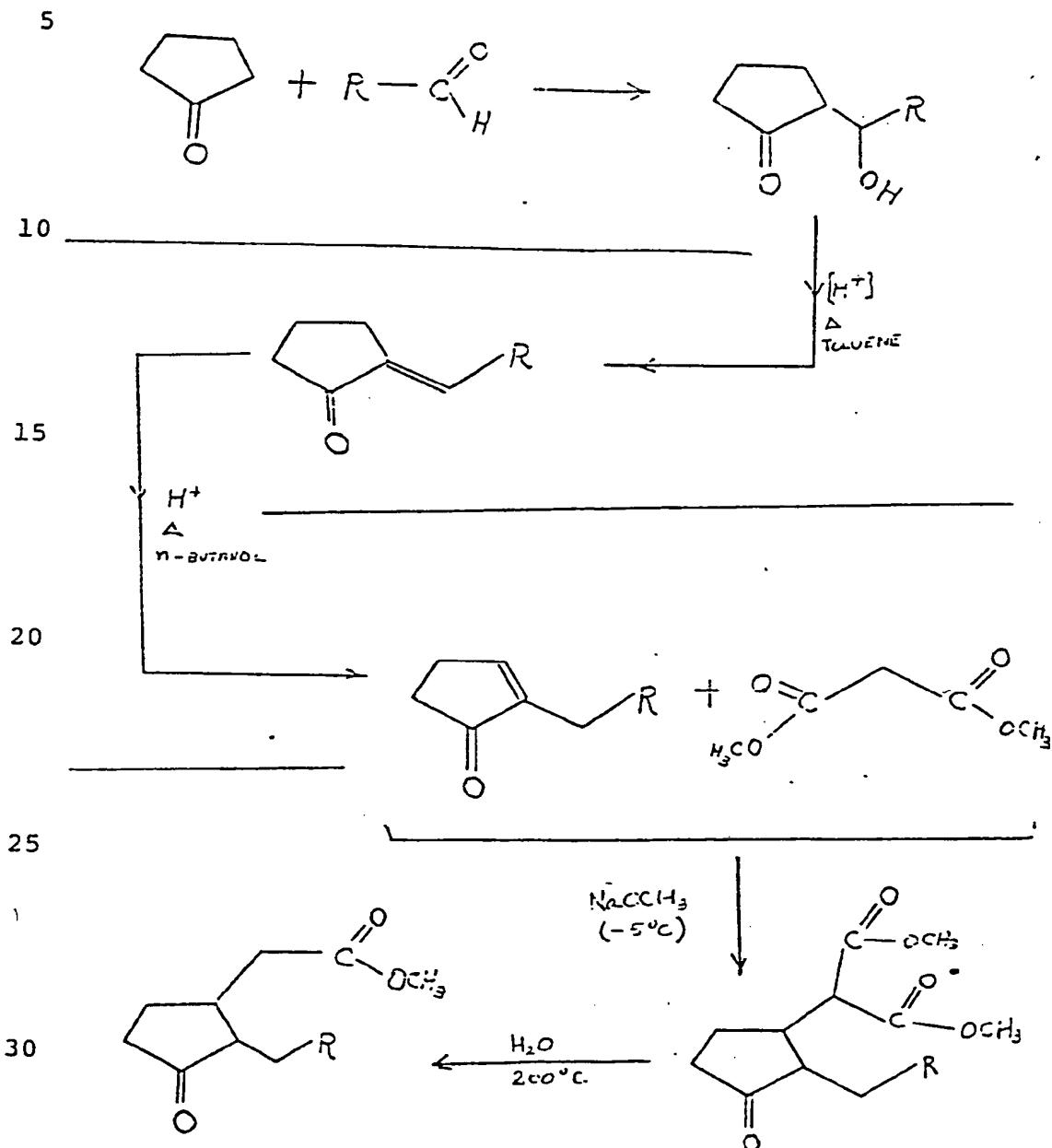


H<sub>2</sub>O  
200°C

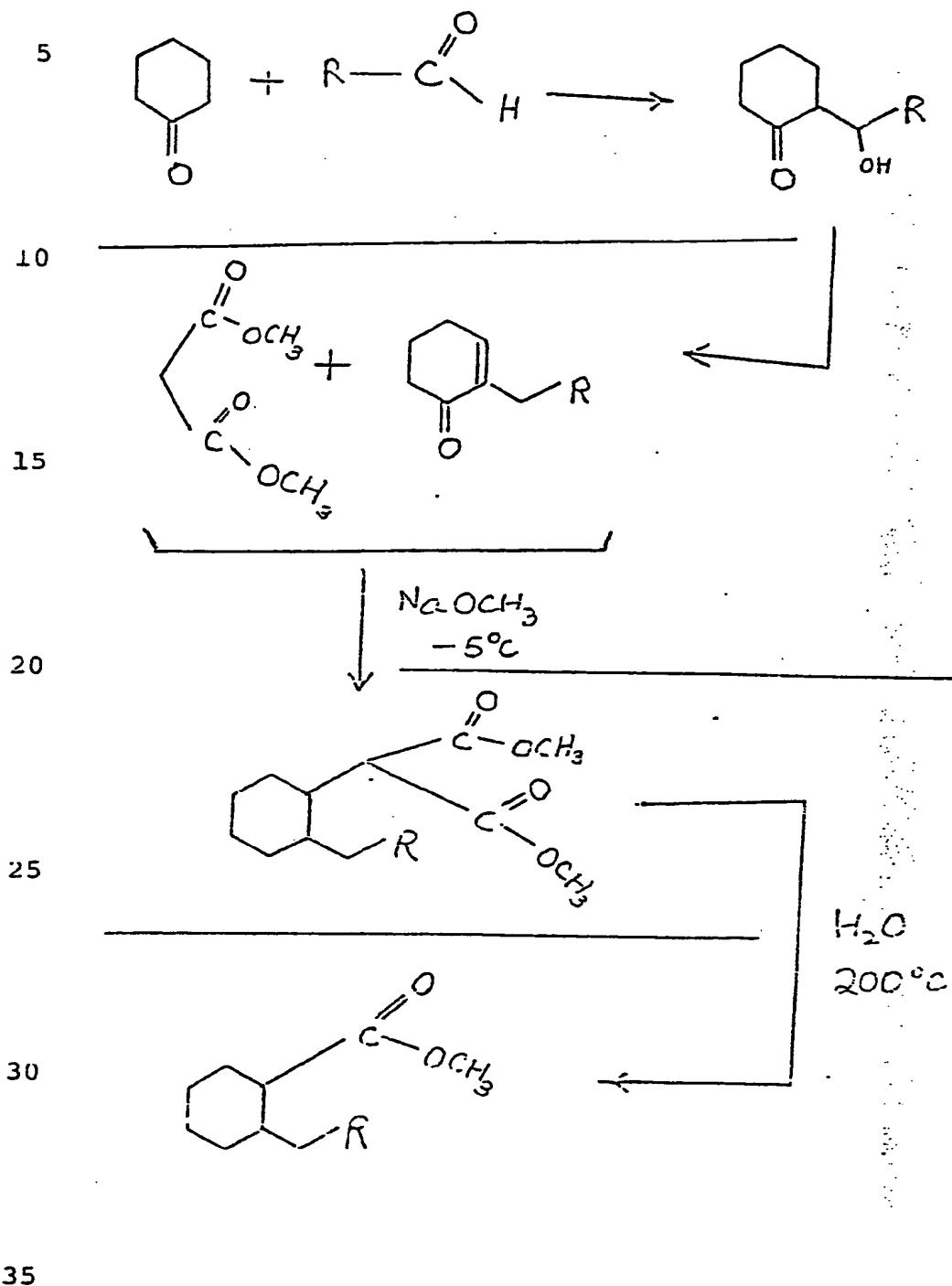


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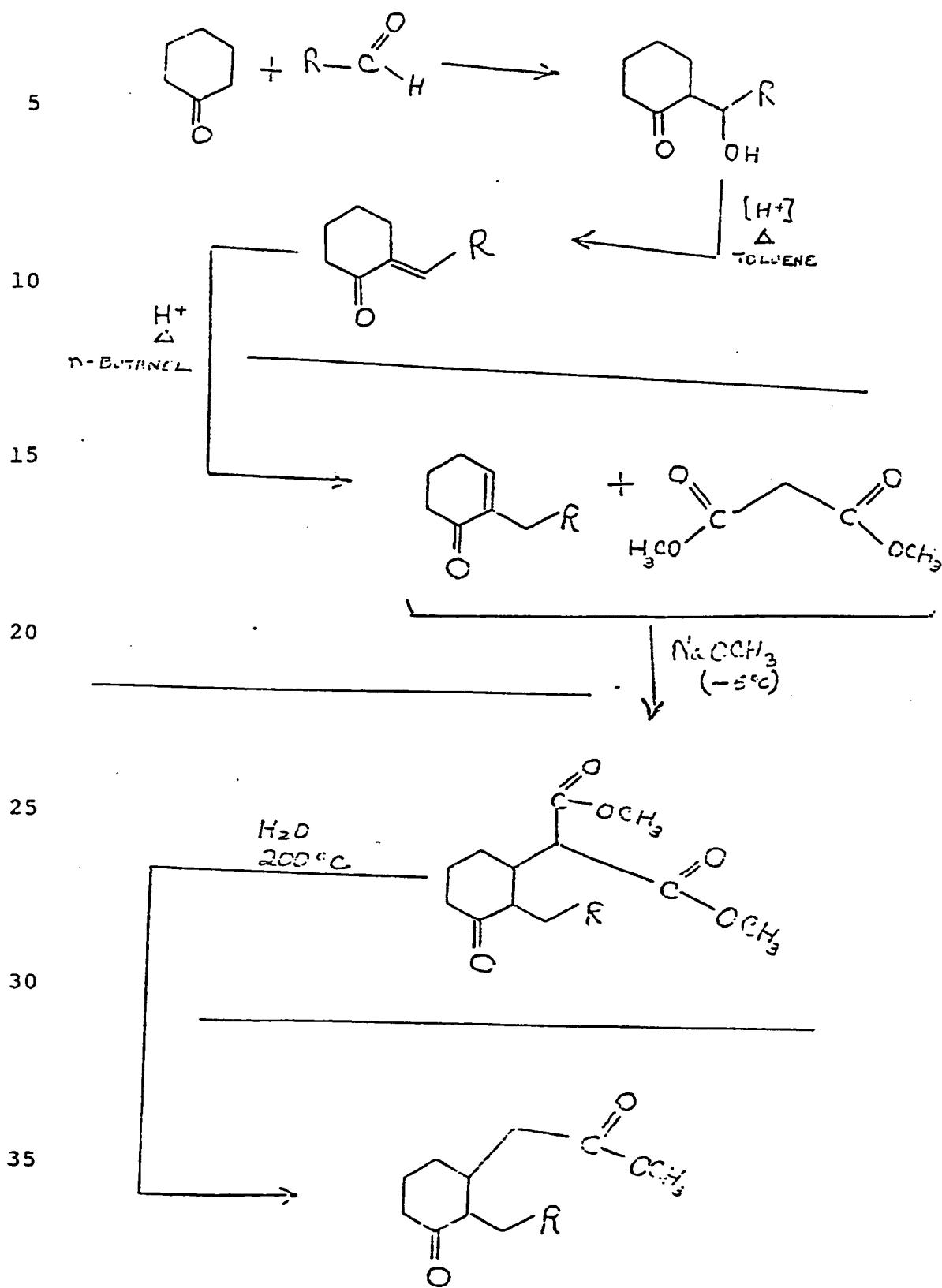
or the reaction scheme:



or the reaction scheme:

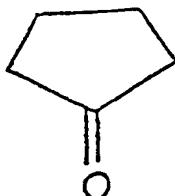


or the reaction scheme:

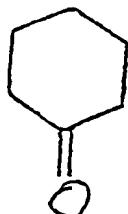


More specifically, the aldol condensation between the cycloalkanone having the structure:

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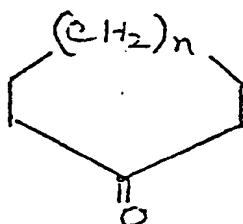
or



or defined according to the structure:

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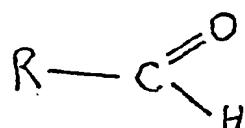
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wherein n is 0 or 1 and the aldehyde having the structure:

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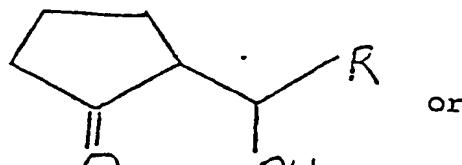


may take place at a temperature of between 20°C and 50°C over a period of time of from about one half hour up to four hours. Preferably, the reaction time is about one hour and the reaction temperature is about 30°C. The mole ratio of cycloalkanone:aldehyde may vary from about 3:1 up to about 1:3 with a preferred mole ratio of 1.8 moles

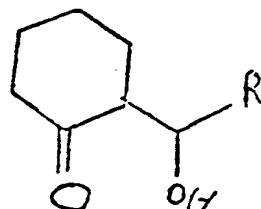
ketone:1 mole aldehyde. The mole ratio of base used (e.g., sodium hydroxide, barium hydroxide or potassium hydroxide):aldehyde may vary from about 0.05 moles base:1 mole aldehyde up to 0.1 mole base:1 mole aldehyde with a 5 preferred mole ratio of 0.083:1.

The reaction of the resulting aldol condensation product having the structure:

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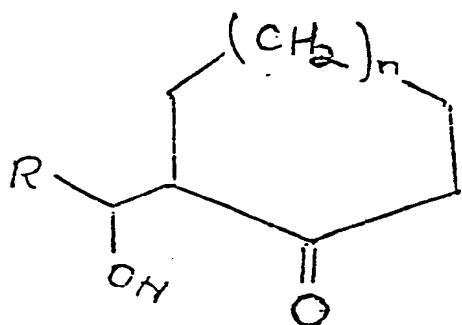
or



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or having the generic structure:

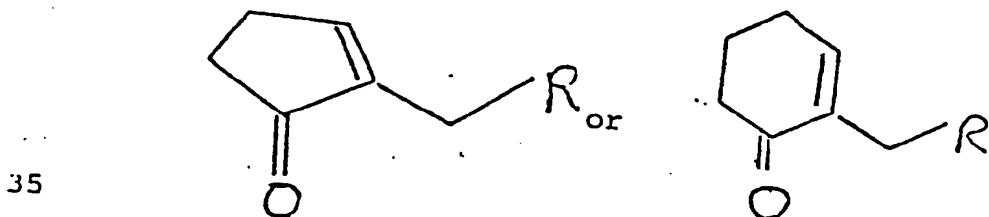
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to form, ultimately, the alkyl cyclopentenone having the structure:

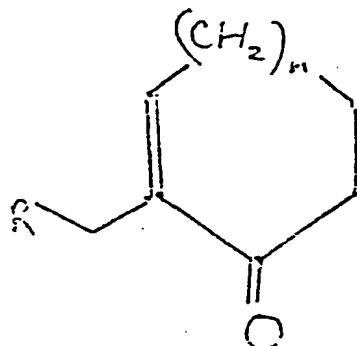
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or having the generic structure:

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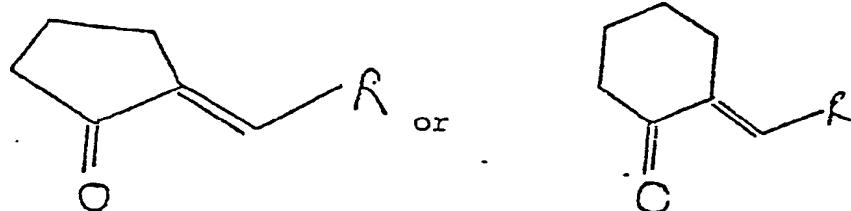


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can either be performed stepwise via the alkylidene cyclopentanone having the structure:

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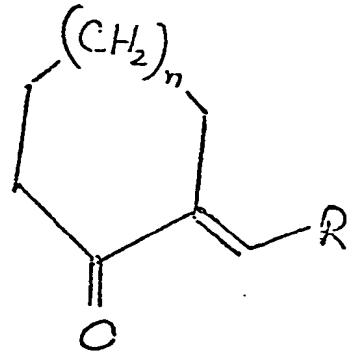


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or having the generic structure:

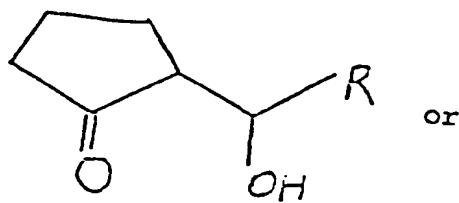
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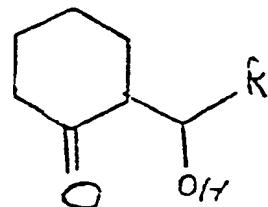


by dehydration with an acid such as oxalic acid followed by endoisomerization with aqueous acid (hydrochloric acid or hydrobromic acid) in refluxing n-butanol or, more preferably, reacting the aldol condensation product  
 5 itself having the structure:

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or

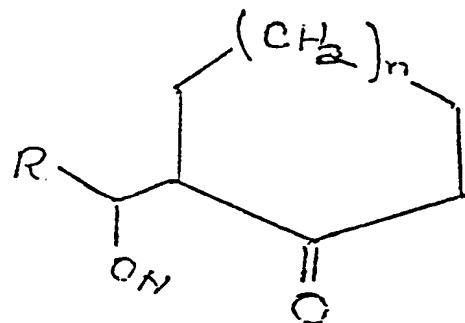


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or having the generic structure:

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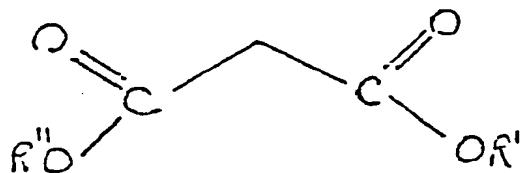


with hydrogen chloride or hydrogen bromide, preferably  
 30 hydrogen bromide in refluxing n-butanol. As will be seen  
 by the examples, using an acid such as para toluene  
 sulfonic acid fails to give rise to an appreciable yield  
 compared with the use of hydrogen chloride or hydrogen  
 bromide.

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The reaction of the malonic acid diester having the structure:

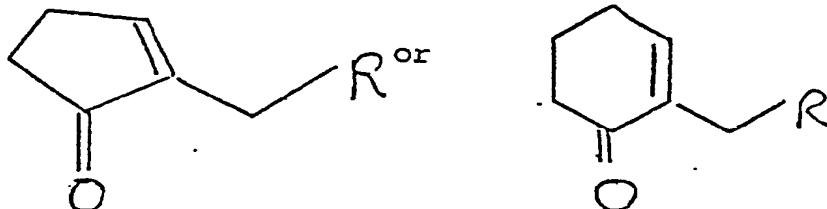
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with the alkyl cyclopentenone having the structure:

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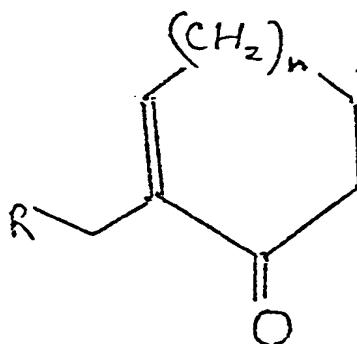


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or having the generic structure:

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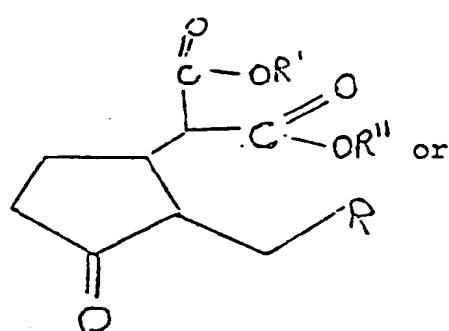
uses ordinary conditions of the Michael Addition synthesis  
35 e.g., takes place in the presence of an alkali metal alko-  
side such as sodium or potassium methoxide or ethoxide or  
propoxide at a temperature in the range of from about

-20°C up to about +10°C with a preferred temperature of about -5°C. The range of conditions may be substantially the same as those described in the analogous reaction in United Kingdom Patent 907,431.

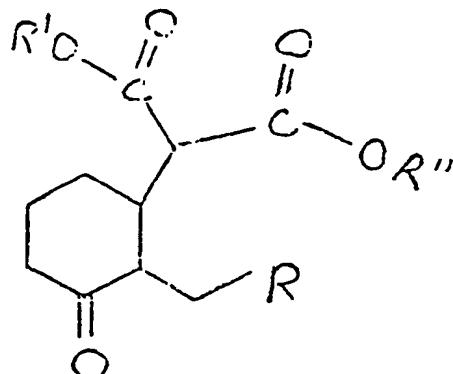
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The resulting malonic ester-cycloalkenone addition product having one of the structure:

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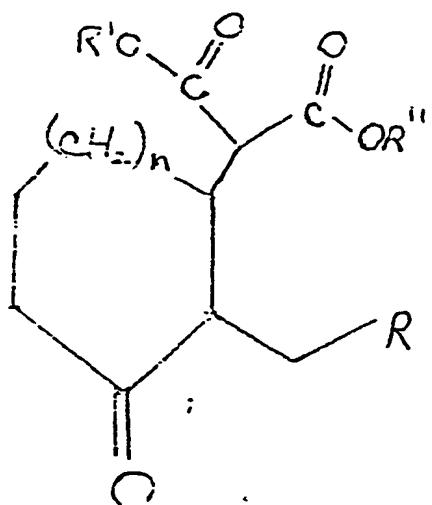
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or defined according to the generic structure:

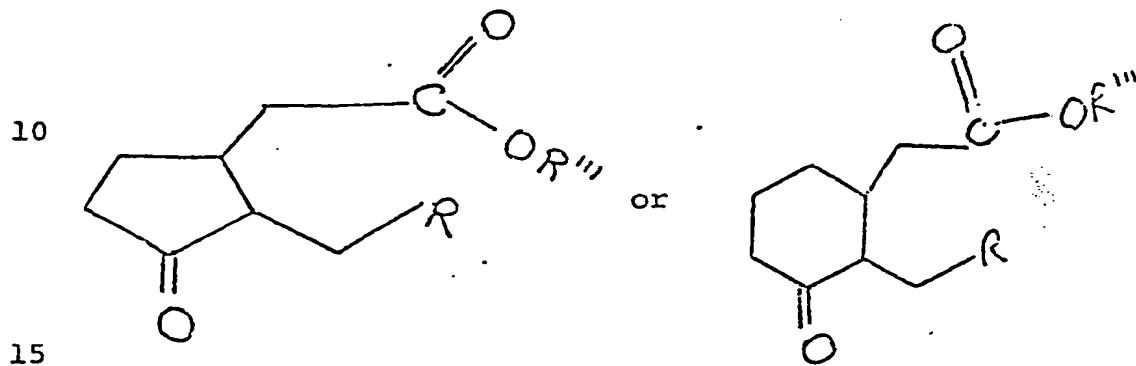
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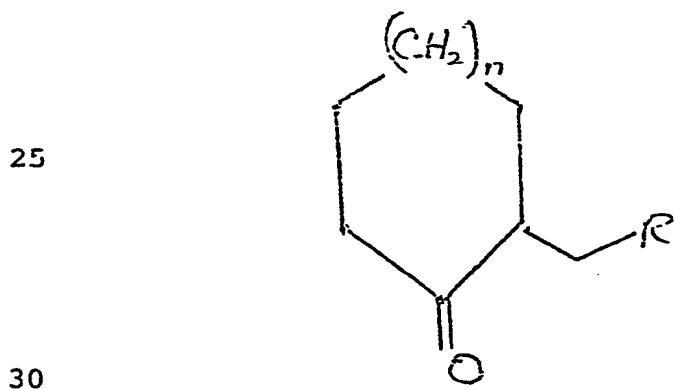
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may then be reacted with water at a temperature in the range of from about 180°C up to about 210°C at pressures of from about 1 atmosphere up to about 10 atmospheres thereby forming the methyl dihydrojasmonate or homologue 5 thereof defined according to the generic structure:



20 or defined according to the generic structure:



This reaction may be carried out according to the procedures set forth in German Offenlengungsschrift 27 32 107 of January 19, 1978.

Alternatively, the malonic ester-cycloalkenone addition product may subsequently be saponified using aqueous alkali metal hydroxide such as sodium hydroxide or potassium hydroxide (20-50% in concentration) and then 5 acidified with hydrochloric acid or acetic acid and finally heated at a temperature in the range of from 150°C up to 200°C thereby causing monodecarboxylation of the resulting dicarboxylic acid. The resulting material may then be re-esterified with methanol using a sulfuric acid 10 catalyst according to standard esterification conditions.

The following Examples I-III and V-VII serve to illustrate embodiments of our invention as it is now preferred to practice it. Example IV illustrates the utility for a 15 compound produced according to a process of our invention. It will be understood that these examples are illustrative and restricted thereto only as defined in the appended claims.

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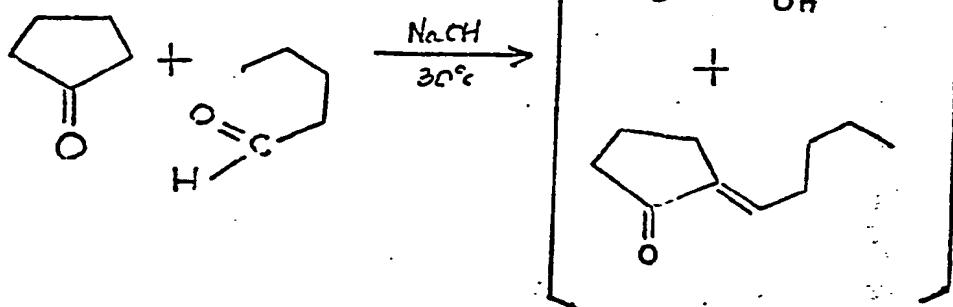
Example I-A

Reaction:

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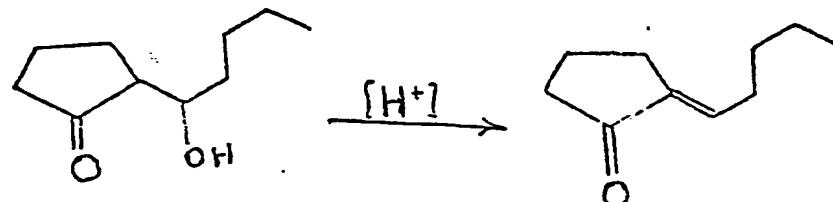


\* \* \* \* \*

Reaction:

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Into a 5-liter reaction flask equipped with mechanical stirrer, 500 ml addition funnel, immersion thermometer and reflux condenser and 5-liter heating mantle and dry ice/isopropyl alcohol bath are charged 16.5 grams of sodium hydroxide and 1500 ml water. The resulting mixture is warmed to  $30^\circ\text{C}$ . 756 grams (9.0 moles) of cyclo-  
35 pentanone is then added dropwise with stirring over a 15 minute period while maintaining the reaction temperature at  $30^\circ\text{C}$  with the dry ice/isopropanol bath.

430 grams (5.0 moles) of n-valeraldehyde is then added dropwise with stirring over a 40 minute period while keeping the temperature at 30°C. After addition, the reaction mass is stirred for a period of 1 hour at 30°C.

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After 1 hour, 30.0 grams of acetic acid is added using a dropping pipette and the reflux condenser is replaced with a splash column equipped with rush-over head. The resulting mixture is then heated and steam distilled.

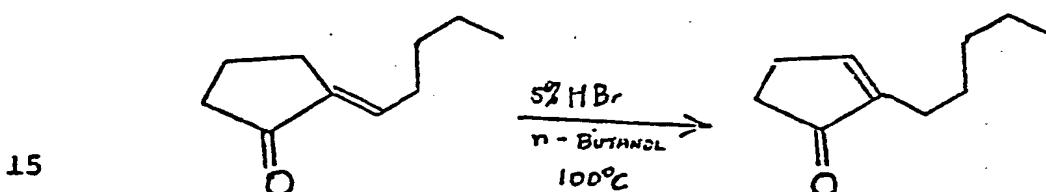
10 All fractions are monitored on a 400' SE-30 glass capillary GLC column. The distillation is shut down when no further apparent oil layer is formed. The resulting mixture is allowed to cool down and poured into a separatory funnel. The aqueous layer is separated and washed  
15 with two volumes of toluene. The toluene layer is combined with the organic layer and the resulting organic layer is washed with two volumes of saturated sodium chloride solution and then filtered through cotton. The resulting material is placed in the 5-liter reaction  
20 flask as equipped above.

10.0 grams of oxalic acid is then added and the reaction mixture is heated with stirring and azeotropically distilling water until no further water is evolved (about  
25 90 ml water being removed). The reaction equipment is then shut down and the reaction mass is cooled and poured into a 4-liter separatory funnel. The reaction mass is then washed with two volumes of saturated sodium chloride solution followed by two volumes of 5% sodium carbonate  
30 solution followed by two volumes of saturated sodium chloride solution. The resulting material is then dried over anhydrous sodium sulfate and concentrated to yield 1120.0 grams of material.

35 The resulting product is then distilled under vacuum using a splash column and rush-over head into 3 fractions with the following results:

Fraction No.	Weight	% Product	Wt. Product	Vapor Temp.	Liq. Temp.	Press. mm Hg
1	137.2	1.2	1.60	27-38	26-106	4.40
2	491.4	86.3	424.1	95	107	0.40
3	162.5	20.2	146.6	106	156	0.60

5

Example I-B10 Reaction:

Into a 5-liter reaction flask equipped with mechanical stirrer, immersion thermometer, bubble condenser and 5-liter heating mantle are charged 570.4 grams (3.75 moles) of 2-pentylidene cyclopentanone prepared according to Example I-A (fractions 1-3 bulked) and 2400 ml of 5% hydrogen bromide in n-butanol (120 ml hydrogen bromide in 2280 ml n-butanol). The resulting mixture is heated with stirring to reflux at 105°C. The reaction mass is then stirred over a period of 115 minutes while monitoring the progress on a 6' x 1/4" glass SE-30 packed column (operated at 150°C isothermal) approximately every 5-10 minutes.

After 115 minutes, the reaction apparatus is shut down and the reaction mass is cooled. The resulting mixture is poured into a separatory funnel and washed with 1 volume of saturated sodium chloride solution followed by 1 volume of 10% sodium carbonate solution and 2 volumes of saturated sodium chloride solution. The resulting material is then dried over anhydrous sodium sulfate and concentrated to yield 788.0 grams of crude product.

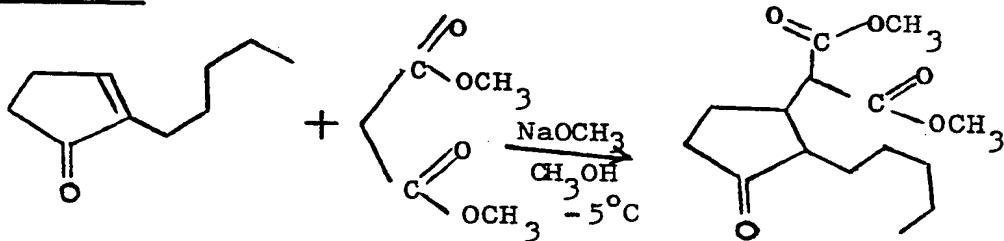
The resulting crude is then distilled under vacuum using a splash column and rush-over head into 3 fractions as follows:

5	Fraction	%	Wt.	Vapor	Liq.	Press.	
	No.	Weight	Product	Product	Temp.	Temp.	mm Hg
10	1	138.85	4.68	6.50	26-35	28-90	1.30
	2	259.92	90.43	235.05	81	102	1.35
	3	224.40	86.72	194.60	87	174	

10

Example I-CReaction:

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Into a 5-liter reaction flask equipped with mechanical stirrer, immersion thermometer, 1000 ml addition funnel with nitrogen inlet and water-cooled condenser with nitrogen bubbler and dry ice/isopropyl alcohol bath is placed 1350 ml of anhydrous methyl alcohol and 7.82 grams (0.34 gm-atoms) of sodium pellets under a nitrogen atmosphere at 25°C. In one batch, 448.8 grams (3.40 moles) of dimethyl malonate is added with stirring while maintaining the reaction mass temperature at 25°C. The reaction mass is then cooled to -5°C.

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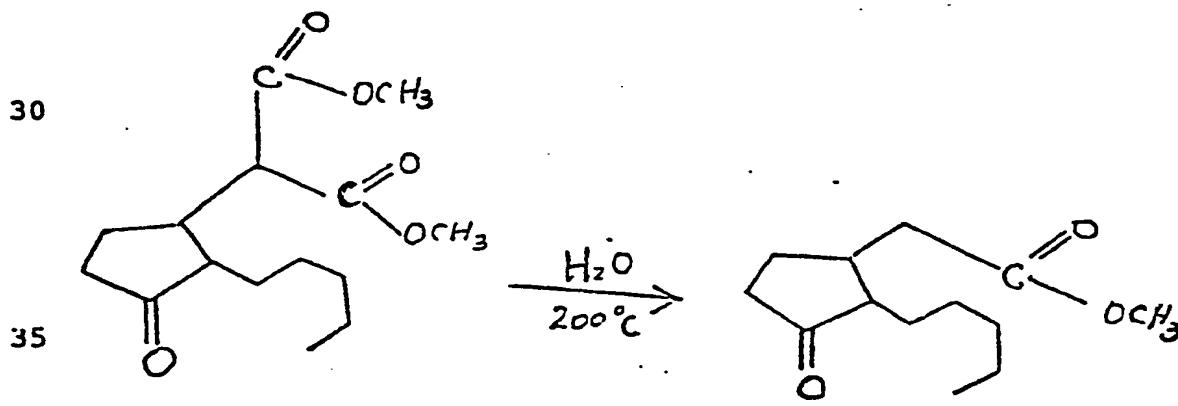
Over a 40 minute period 429.65 grams (2.83 moles) of 2-pentyl-2-cyclopent-1-one prepared according to Example I-B is added. The reaction mass is then stirred for a period of 1 hour at -5°C. 40.8 grams (0.68 moles) of acetic acid is then added to the reaction mass and the reaction mixture is stirred and permitted to attain room temperature. The reaction mass is then transferred to a large separatory funnel. Approximately 2 liters of water is added to the reaction mass and the resulting mixture is shaken vigorously. The oil layer separates to the bottom and is removed and retained.

The aqueous layer is then stripped to remove the methanol; washed with 2 volumes of diethyl ether and discarded.

15. The diethyl ether washings are combined with the organic layer (the oil layer), washed two times with saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The resulting dried material is concentrated to yield 1271 grams of crude material. GLC  
20 analysis on a 6' x 1/4" SE-30 packed glass column shows the crude to be 40.34% diester (512.72 grams = 63.79% yield).

25 Example I-D

Reaction:



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Into a 3-liter reaction flask equipped with mechanical stirrer, immersion thermometer, 250 ml addition funnel with nitrogen inlet, 1-ft. jacketed column packed with saddles, a rush-over head with thermometer, a take-off 5 adapter with nitrogen bubbler, a 500 ml receiver and a heating mantle is placed 1271.0 grams of the crude 3-dimethylmalonyl-2-pentylcyclopent-1-one prepared according to Example I-C. The compound is heated with stirring to 200°C. During the heating, any solvent from 10 the previous reaction of Example I-C distills over and is discarded. At 200°C, 50.94 grams (2.83 moles) of water is added dropwise (1 drop per 1.5 seconds) causing a vigorous evolution of carbon dioxide and methyl alcohol which is collected in the receiver. The addition takes 15 approximately 1 hour. Heating at 200°C is continued for 35 minutes. The reaction is monitored by GLC (6' x 1/4" SE-30 packed glass column) immediately after the water addition and 35 minutes later. Substantial diester still remains so an additional 10 grams of water is 20 added over a 20 minute period and the reaction mass is again stirred for 30 minutes. GLC analysis continues to show diester as the reaction is shut down for 12 hours and recommenced when an additional 10 grams of water is added at 200°C over a 20 minute period. Stirring is 25 continued at 200°C for an additional 30 minutes. At this point, GLC analysis indicates no diester is present and the reaction apparatus is shut down and the reaction mass cooled to room temperature.

30 The crude material (664 grams) is then distilled under vacuum on a 2" splash column with rush-over head into four fractions as follows:

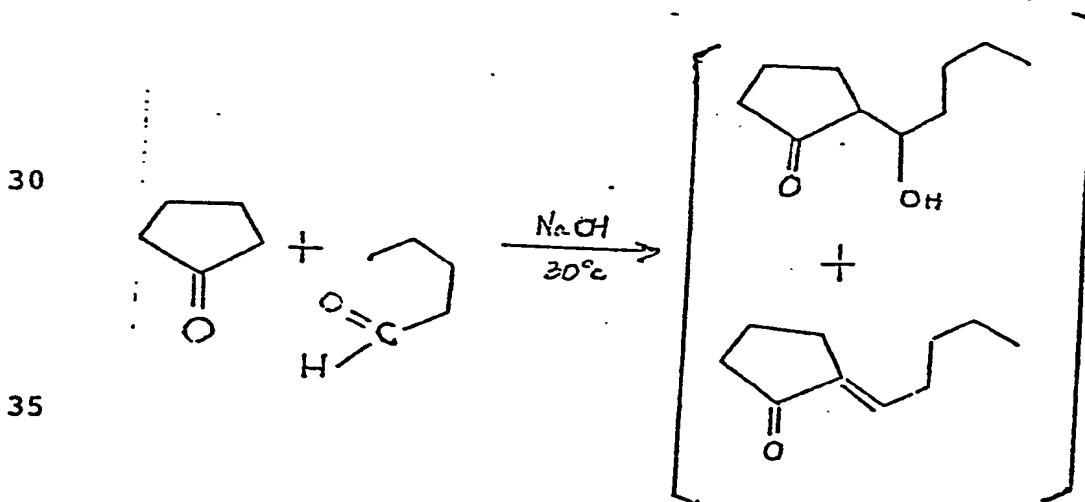
Fraction No.	Weight	% Product	Wt. Product	Vapor Temp.	Liq. Temp.	Press. mm Hg
1	64.07	4.67	2.99	112	134	0.35
2	239.66	75.04	179.84	112	134	0.35
3	306.74	96.33	301.62	112	136-139	0.30-0.33
5	28.30	89.77	25.41	112	148-200	0.30

Fractions 2, 3 and 4 are bulked and fractionally distilled on a 12" Hemple Column having Goodloe packing. The distillation is such that the material is distilled 10 into 11 fractions as follows:

Fraction No.	Weight	% Product	Wt. Product	Vapor Temp.	Liq. Temp.	Press. mm Hg	Reflux Ratio
1	13.37			51-53	125-136	0.19	4:1
2	18.22			58	137.5	0.15	4:1
3	5.43			85	138	0.18	4:1
15	17.62	93.58	16.49	80-103	137-140	0.16	4:1
4	12.02	98.35	11.82	101	146	0.16	4:1
5	72.75	99.41	72.32	105	152	0.16	1:1
6	77.05	99.52	76.68	108	156	0.16	1:1
7	105.63	99.49	105.09	109	159	0.16	1:1
8	77.33	99.44	76.90	109	162	0.16	1:1
9	96.83	98.56	95.44	109	182	0.16	1:1
20	37.90	90.88	34.44	139	220	0.16	1:1

### Example II-A

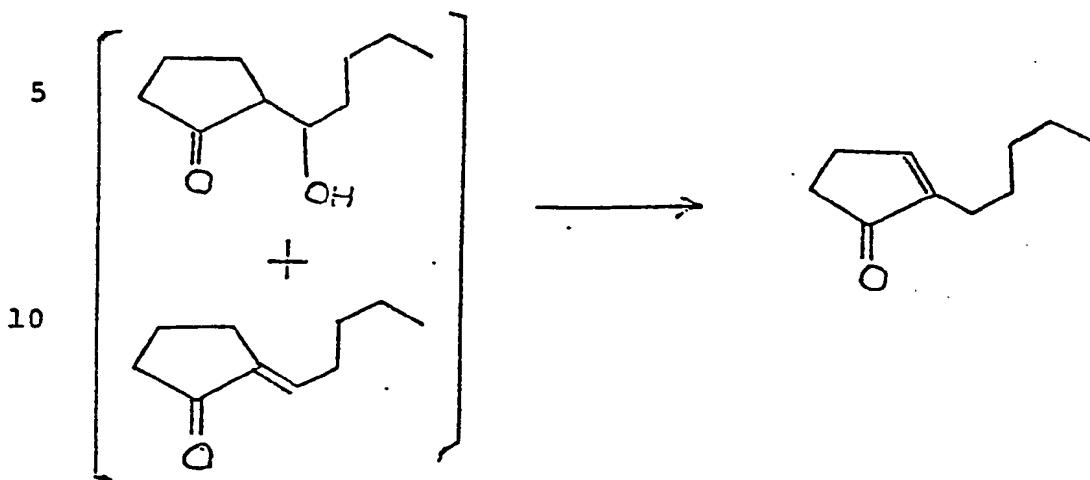
#### 25 Reaction:



Into a 500 ml reaction flask equipped with mechanical stirrer, immersion thermometer, 150 ml addition funnel, water-cooled condenser, heating mantle and ice bath is placed 1.65 grams of sodium hydroxide pellets and 155 ml 5 water. The resulting solution is warmed to 30°C.

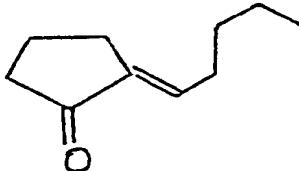
75.6 grams (0.9 moles) of cyclopentanone is then added dropwise with stirring while maintaining the temperature at 30-31°C. 43.0 grams (0.5 moles) of n-valeraldehyde is then added dropwise with stirring over a period of 10 about 30 minutes while maintaining the temperature at 30°C. The reaction mass is then stirred for 1 hour at 30°C. At this point, 3.0 grams of acetic acid and 100 ml of water are added. The condenser is then replaced with a splash column and rush-over head and the reaction mass 15 is heated to 95°C to distill the unreacted cyclopentanone. The reaction mass is then distilled until the head temperature is 100°C and the majority of the cyclopentanone is removed. The reaction apparatus is then shut down and the reaction mass is cooled and poured into a 20 separatory funnel.

The oil layer is taken up in diethyl ether and separated from the aqueous layer. It is then washed with 1 volume of saturated sodium chloride solution and dried over 25 anhydrous sodium sulfate and concentrated to yield 77.46 grams of crude product.

Example II-BReaction:

15 Into a 250 ml reaction flask equipped with mechanical stirrer, immersion thermomether, water-cooled condenser and heating mantle are charged 38.73 grams (0.23 moles) of the aldol condensation product produced according to Example III-A and 138.6 ml of 5% hydrogen bromide in  
 20 n-butanol (6.60 ml of 48% of HBr in 132 ml n-butanol).  
 The reaction mixture is heated to reflux (102°C) and maintained at reflux (monitoring by GLC) until all of the isomer having the structure:

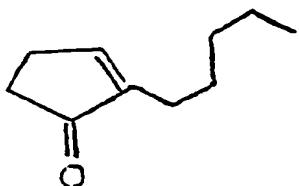
25



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is isomerized to the product having the structure:

35



in a ratio of 14:1 endo:exo (87.9% endo:6.3% exo). The reaction apparatus is then shut down and the reaction mass is cooled and poured into a separatory funnel. The oil layer is then washed with 1 volume of saturated sodium chloride solution; followed by 1 volume of 10% sodium carbonate solution; followed by 3 volumes of saturated sodium chloride solution. The resulting material is then dried over anhydrous sodium sulfate and the crude material (186.61 grams) is distilled under 10 vacuum into 2 fractions as follows:

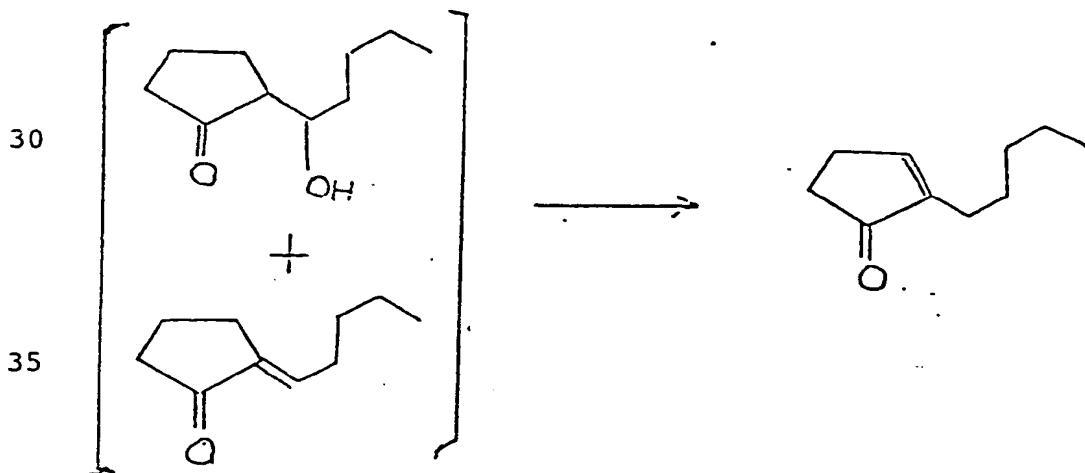
15	<u>Fraction No.</u>	<u>Weight</u>	<u>% Product</u>	<u>Wt. Product</u>	<u>Vapor Temp.</u>	<u>Liq. Temp.</u>	<u>Press. mm Hg</u>
	1	155.8	0.29	0.45	20-22	85-90	1.6
	2	20.3	85.25	17.31	75	135	1.6

20

Yield of product is 17.76 grams (50.80%).

### Example II-C

#### Reaction:



Into a 250 ml reaction flask equipped with mechanical stirrer, immersion thermometer, water-cooled condenser and heating mantle is placed 38.73 grams (0.23 moles) of the aldol condensation product of cyclopentanone and 5 n-valeraldehyde produced according to Example II-A and 176.4 ml of 5% hydrogen chloride in n-butanol (8.4 ml of 38% HCl in 168 ml n-butanol). The reaction mass is heated with stirring to reflux and refluxed until the ratio of endo:exo isomer is 13:1 (87.4% endo:6.7% exo) 10 monitored on a 6' x 1/4" SE-30 glass packed GLC column).

The time of reaction is 165 minutes. At the end of the 165-minute period the reaction apparatus is shut down and the reaction mass is washed with 1 volume of saturated sodium chloride solution followed by 1 volume of 10% 15 sodium carbonate solution and 3 volumes of saturated sodium chloride solution. The product is then dried over anhydrous sodium sulfate to yield 249 grams of crude. The crude material is distilled under vacuum over a rush-over head as follows:

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Fraction No.	Weight	% Product	Wt. Product	Vapor Temp.	Loc. Temp.	Press. mm Hg
1	142.63	0.44	0.63	20-22	92-95	1.5
2	19.45	87.57	17.03	56	185	3.40

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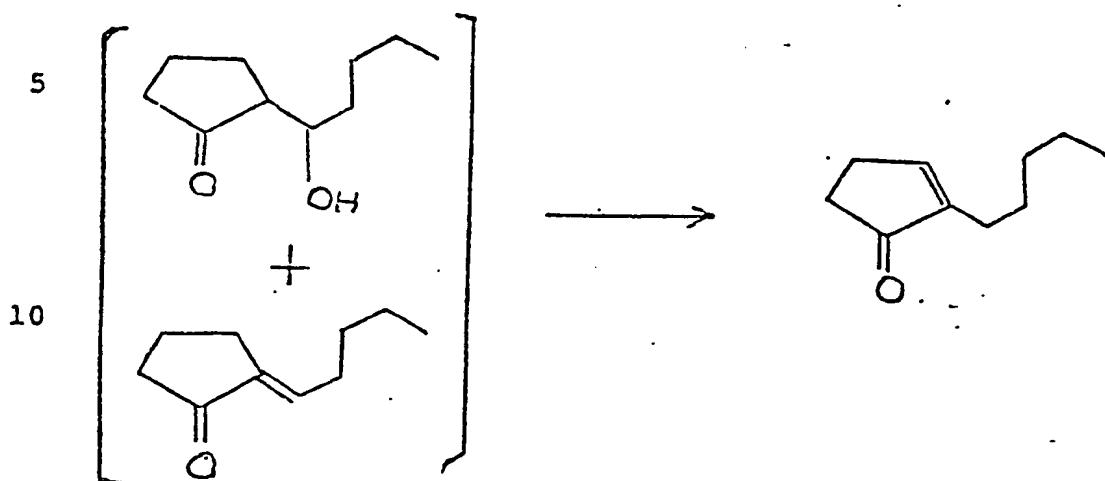
Yield of product is 17.66 grams (50.52%)

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Example II-D

Attempted Reaction:



15 Into a 250 ml reaction flask equipped with mechanical stirrer, Dean-Stark trap with Friedrich's condenser, immersion thermometer and heating mantle is placed 20.0 grams (0.12 moles) of the cyclopentanone-n-valer-aldehyde aldol condensation product produced according  
20 to Example II-A; 100 ml toluene and 2.28 grams (0.012 moles) of paratoluene sulfonic acid. The reaction mass is heated to reflux (114°C) with stirring and approximately 2.6 ml water was azeotropically distilled from the reaction mass. The reaction is carried on for about 140  
25 minutes and then the apparatus is shut down overnight for a period of 12 hours. The reaction is then restarted and run for 120 minutes additional time. The reaction mass is monitored on a 6' x 1.4" SE-30 GLC column until sufficient conversion appears to take place (91.6% endo:  
30 3.7% exo). The apparatus is shut down and the reaction product is cooled to room temperature.

The reaction product is washed with 1 volume of saturated sodium chloride solution; 2 volumes of 5% sodium carbonate  
35 solution; and 2 volumes of saturated sodium chloride solution. The product is then dried over anhydrous sodium sulfate and concentrated to yield 15.46 grams of crude

material. The crude is then rush-over distilled under vacuum into fractions as follows:

Fraction No.	Weight	% Product	Wt. Product	Vapor Temp.	Liq. Temp.	Press. mm Hg
5	1	1.22	50.99	1.11	25-26	28-205

Yield of product is 1.11 grams (6.09%).

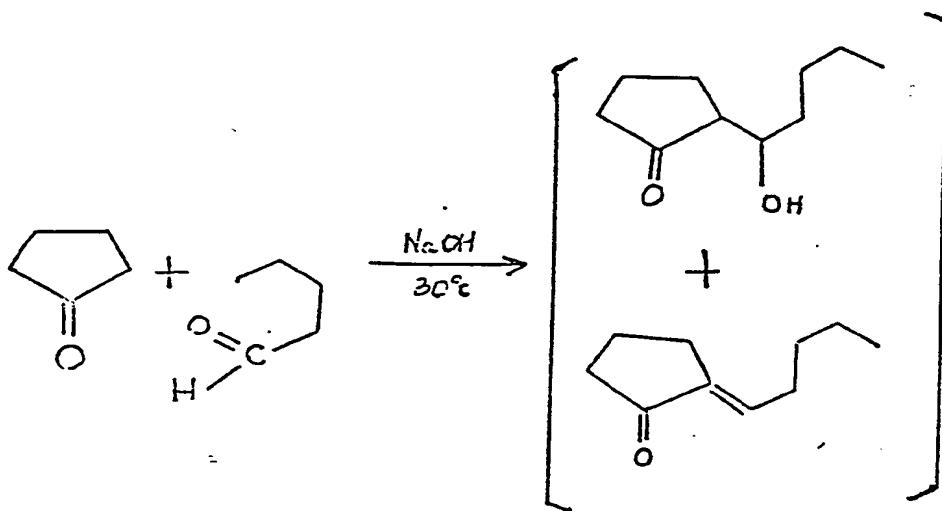
10 Example III

Reaction:

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Into a 5-liter reaction flask equipped with mechanical stirrer, 500 ml addition funnel, immersion thermometer, Friedrich's condenser, heating mantle and dry ice/isopropyl alcohol bath are placed 1.5 liters of water and 5 16.5 grams of sodium hydroxide. The resulting solution is warmed to 30°C. 756 grams (9.0 moles) of cyclopentanone is added dropwise with stirring while maintaining the temperature at 30°C. After addition of the cyclopentanone, 430 grams (5.0 moles) of n-valeraldehyde 10 was added dropwise with stirring keeping the temperature at 30°C using the isopropyl alcohol/dry ice bath as needed. The reaction mass is then stirred for a period of 1 hour at 30°C.

15 After 1 hour, 30.0 grams of acetic acid is added from a dropping pipette while maintaining the temperature at 30°C and stirring the reaction mass for 2-3 minutes thus obtaining in the reaction mass a pH of 6. The reaction apparatus is then shut down and the reaction mass is 20 poured into a separatory funnel where the water and oil layers are separated. The water layer is washed with 2 volumes toluene and the toluene layer is combined with the oil layer and the washed aqueous layer is discarded. The organic layer is then washed with 2 volumes of 25 saturated sodium chloride solution and filtered through cotton. The resulting organic material is then charged into a 5-liter reaction flask equipped with mechanical stirrer, Bidwell trap with bubble condenser, immersion thermometer and heating mantle and 10.0 grams of oxalic 30 is added to the reaction mass. The resulting mixture is heated to reflux with stirring and water is azeotropically distilled until no further water is evolved (about 9 hours). 95 ml water is recovered. The resulting mixture is then cooled to room temperature and poured into a 35 separatory funnel. The organic layer is washed with 2 volumes of saturated sodium chloride solution followed

by 1 volume of 5% sodium carbonate solution, followed by 2 volumes of saturated sodium chloride solution. The resulting organic material is dried over anhydrous sodium sulfate and concentrated to yield 582 grams of crude product. This material is distilled in vacuo using a 2" splash column and rush-over head into five fractions as follows:

	<u>Fraction No.</u>	<u>Weight</u>	<u>% Product</u>	<u>Wt. Product</u>	<u>Vapor Temp.</u>	<u>Liq. Temp.</u>	<u>Press. mm Hg</u>
10	1	201.94	1.31	2.65	27-32	38-109	2.80
	2	159.85	90.59	144.81	27	94	0.22
	3	252.28	93.75	236.51	26-80	26-107	0.24
	4	225.34	86.94	195.91	93	149	0.43
	5	15.88	17.06	2.71	100	170	0.43

15 Yield of product is 582.59 grams (76.66%).

#### Example IV

#### Jasmine Perfume

20 The following mixture is prepared:

	<u>Ingredients</u>	<u>Parts by Weight</u>
	Para Cresol	1
	Acetyl Methyl Anthranilate	20
	Farnesol	4
25	Cis-3-hexenyl benzoate	30
	Nerolidol	30
	Indol	15
	Eugenol	20
	Benzyl Alcohol	40
30	Methyl Linoleate	40
	Jasmin Lactone	20
	Dihydromethyl Jasmonate	10
	Linalool	150
	Benzyl Acetate	400
35	Abietyl Alcohol	150
	Methyl dihydrojasmonate (Produced according to Example I-D; bulked fractions 5-10)	50

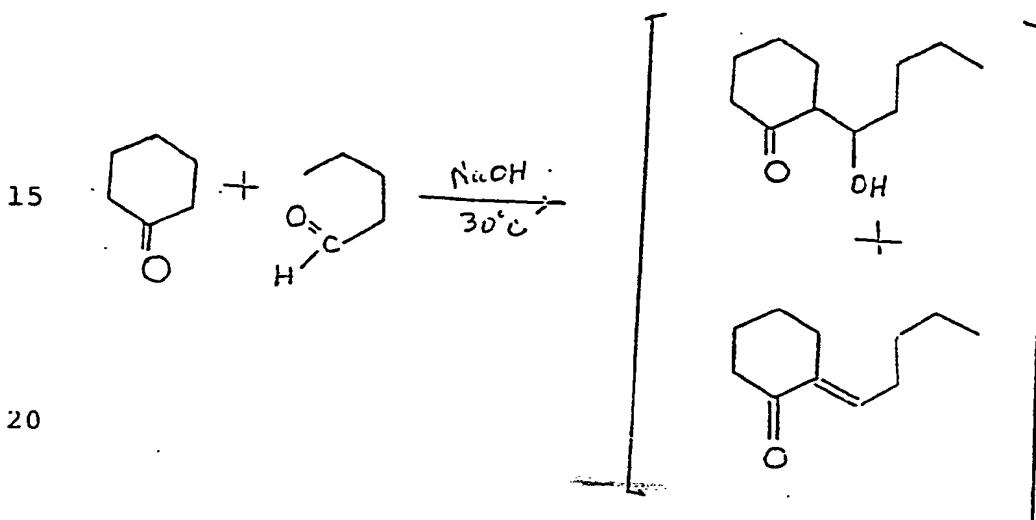
The methyl dinydrojasmonate produced according to Example I-D imparts to this jasmine formulation the green, sweet, floral note so important to the jasmine perfume formulation.

5

### Example V-A

### **Reaction:**

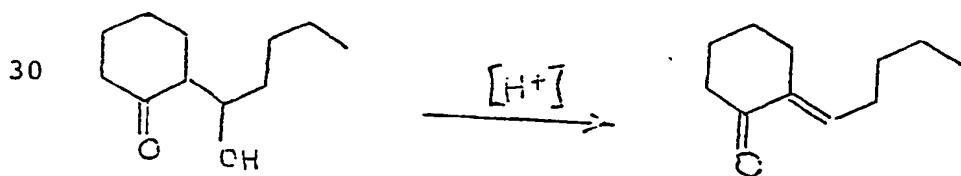
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### Reaction:



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Into a 5-liter reaction flask equipped with mechanical stirrer, 500 ml addition funnel, immersion thermometer and reflux condenser and 5-liter heating mantel and dry ice/isopropyl alcohol bath are charged 16.5 grams 5 of sodium hydroxide and 1500 ml water. The resulting mixture is warmed to 30°C. 882 grams (9.0 moles) of cyclohexanone is then added dropwise with stirring over a 15 minute period while maintaining the reaction temperature at 30°C with the dry ice/isopropanol bath.

10

430 grams (5.0 moles) of n-valeraldehyde is then added dropwise with stirring over a 40 minute period while keeping the temperature at 30°C. After addition, the reaction mass is stirred for a period of 1 hour at 30°C.

15

After 1 hour, 30.0 grams of acetic acid is added using a dropping pipette and the reflux condenser is replaced with a splash column equipped with rush-over head. The resulting mixture is then heated and steam distilled.

20

All fractions are monitored on a 400' SE-30 glass capillary GLC column. The distillation is shut down when no further apparent oil layer is formed. The resulting mixture is allowed to cool down and poured into a separatory funnel. The aqueous layer is separated and 25 washed with two volumes of toluene. The toluene layer is combined with the organic layer and the resulting organic layer is washed with two volumes of saturated sodium chloride solution and then filtered through cotton. The resulting material is placed in the 5-liter reaction 30 flask as equipped above.

10.0 grams of oxalic acid is then added and the reaction mixture is heated with stirring and azeotropically distilling water until no further water is evolved (about 35 90 ml water being removed). The reaction equipment is then shut down and the reaction mass is cooled and poured into a 4-liter separatory funnel. The reaction mass is

then washed with two volumes of saturated sodium chloride solution followed by two volumes of 5% sodium carbonate solution followed by two volumes of saturated sodium chloride solution. The resulting material is then dried 5 over anhydrous sodium sulfate and concentrated to yield 1120.0 grams of material.

The resulting product is then distilled under vacuum using a splash column and rush-over head.

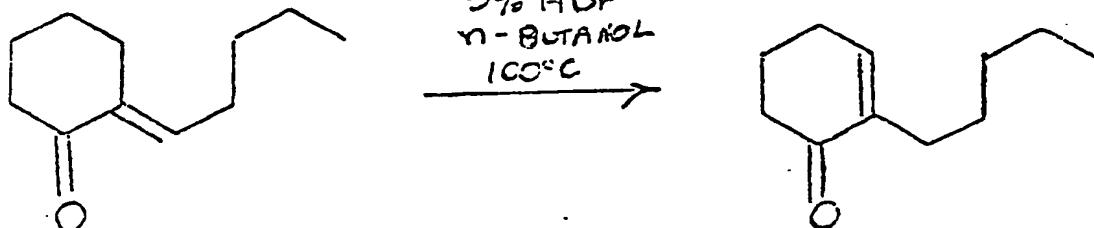
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Example V-B

Reaction:

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Into a 5-liter reaction flask equipped with mechanical 25 stirrer, immersion thermometer, bubble condenser and 5-liter heating mantel are charged 581.3 grams (3.75 moles) of 2-pentylidene cyclohexanone prepared according to Example V-A and 2400 ml of 5% hydrogen bromide in n-butanol (120 ml hydrogen bromide in 2280 ml n-butanol).

30 The resulting mixture is heated with stirring to reflux at 105°C. The reaction mass is then stirred over a period of 115 minutes while monitoring the progress on a 6' x 1/4" glass SE-30 packed column (operated at 150°C isothermal) approximately every 5-10 minutes.

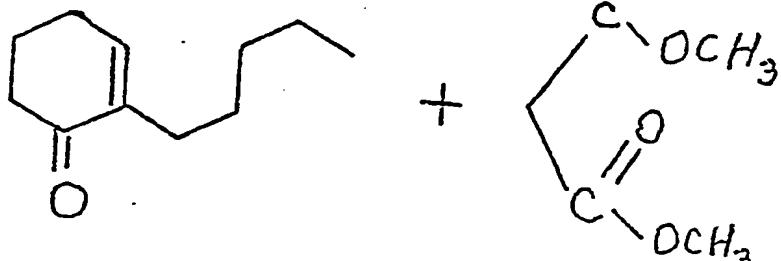
35

After 115 minutes, the reaction apparatus is shut down and the reaction mass is cooled. The resulting mixture is poured into a separatory funnel and washed with 1 volume of saturated sodium chloride solution followed by 5 l volume of 10% sodium carbonate solution and 2 volumes of saturated sodium chloride solution. The resulting material is then dried over anhydrous sodium sulfate and concentrated to yield 795 grams of crude product. The resulting crude is then distilled under vacuum using 10 a splash column and rush-over head.

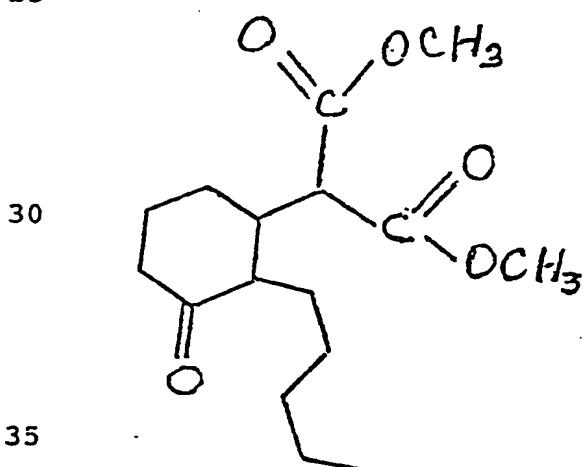
Example V-C

Reaction:

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$\text{NaOCH}_3$   
 $\text{CH}_3\text{OH}$   
[-5°C]

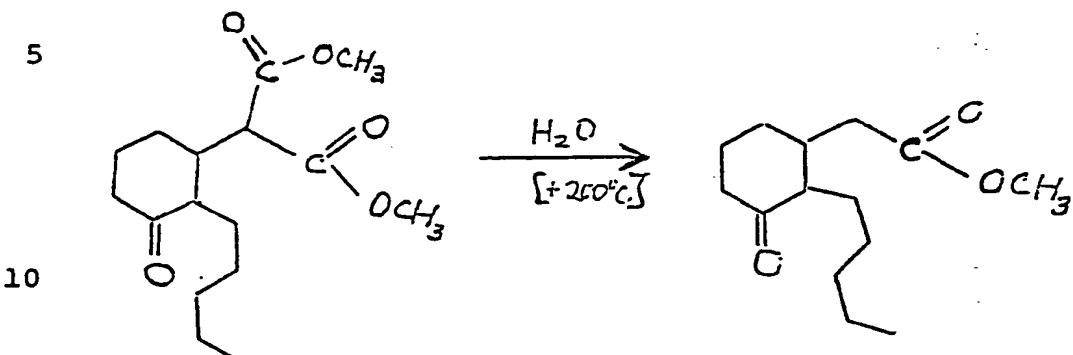
30

35

Into a 5-liter reaction flask equipped with mechanical stirrer, immersion thermometer, 1000 ml addition funnel with nitrogen inlet and water-cooled condenser with nitrogen bubbler and dry ice/isopropyl alcohol bath is  
5 placed 1350 ml of anhydrous methyl alcohol and 7.82 grams (0.34 gm-atoms) of sodium pellets under a nitrogen atmosphere at 25°C. In one batch, 448.8 grams (3.40 moles) of dimethyl malonate is added with stirring while maintaining the reaction mass temperature at 25°C. The  
10 reaction mass is then cooled to -5°C.

Over a 40 minute period 492 grams (3.00 moles) of 2-pentyl-2-cyclohexen-1-one prepared according to Example V-B is added. The reaction mass is then stirred  
15 for a period of 1 hour at -5°C. 40.8 grams (0.68 moles) of acetic acid is then added to the reaction mass and the reaction mixture is stirred and permitted to attain room temperature. The reaction mass is then transferred to a large separatory funnel. Approximately 2 liters of  
20 water is added to the reaction mass and the resulting mixture is shaken vigorously. The oil layer separates to the bottom and is removed and retained.

The aqueous layer is then stripped to remove the methanol;  
25 washed with 2 volumes of diethyl ether and discarded. The diethyl ether washings are combined with the organic layer (the oil layer), washed two times with saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The resulting dried material is concentrated  
30 to yield 1271 grams of crude material. GLC analysis on a 6' x 1/4" SE-30 packed glass column shows the crude to be 40.34% diester (512.72 grams = 63.79% yield).

Example V-DReaction:

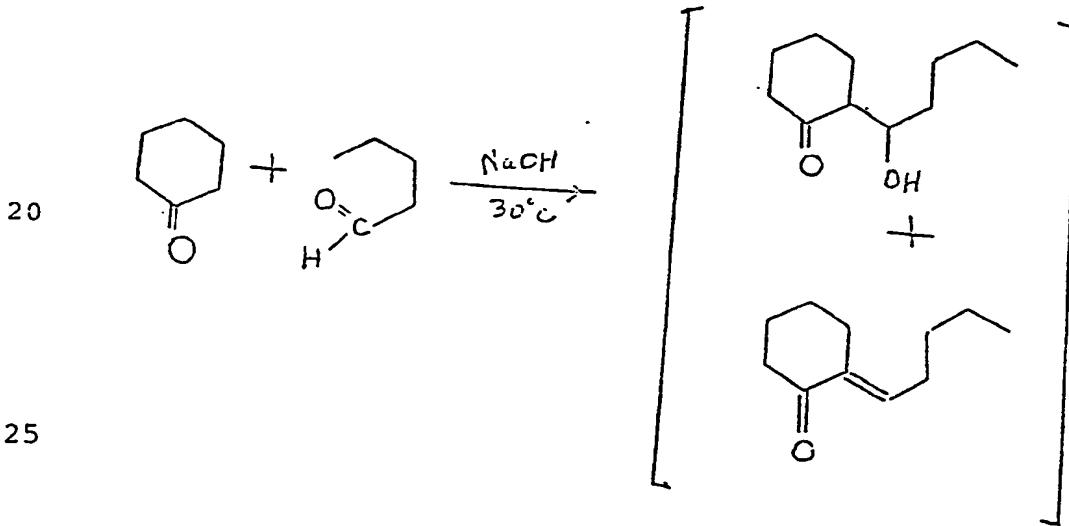
Into a 3-liter reaction flask equipped with mechanical stirrer, immersion thermometer, 250 ml addition funnel with nitrogen inlet, 1-ft. jacketed column packed with saddles, a rush-over head with thermometer, a take-off adapter with nitrogen bubbler, a 500 ml receiver and a heating mantle is placed 1280.0 grams of the crude 15 3-dimethylmalonyl-2-pentyl-cyclohexan-1-one prepared according to Example V-C. The compound is heated with stirring to 200°C. During the heating, any solvent from the previous reaction of Example V-C distills over and is discarded. At 200°C, 50.94 grams (2.83 moles) of 20 water is added dropwise (1 drop per 1.5 seconds) causing a vigorous evolution of carbon dioxide and methyl alcohol which is collected in the receiver. The addition takes approximately 1 hour. Heating at 200°C is continued for 35 minutes. The reaction is monitored by GLC 25 (6' x 1/4" SE-30 packed glass column) immediately after the water addition and 35 minutes later. Substantially diester still remains so an additional 10 grams of water is added over a 20 minute period and the reaction mass is again stirred for 30 minutes. GLC analysis continues 30 to show diester as the reaction is shut down for 12 hours and recommenced when an additional 10 grams of water is added at 200°C over a 20 minute period. Stirring is 35

continued at 200°C for an additional 30 minutes. At this point, GLC analysis indicates no diester is present and the reaction apparatus is shut down and the reaction mass cooled to room temperature. The crude material 5 (640 grams) is then distilled under vacuum on a 2" splash column with rush-over head. The resulting fractions are then fractionally distilled on a 12" Hemple Column having a Goodloe packing. The distillation yields the resulting product in 11 fractions.

10

Example VI-AReaction:

15



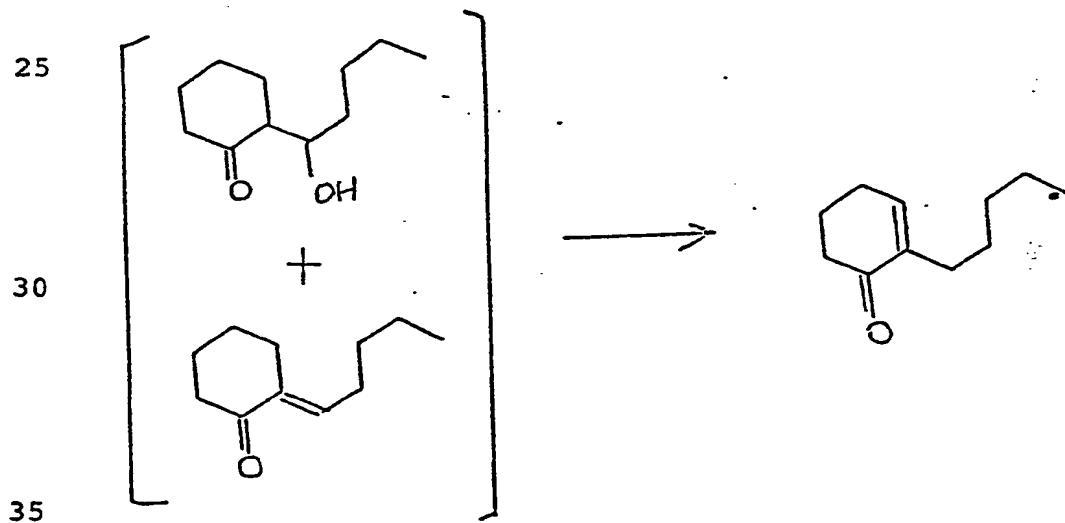
25

30 Into a 500 ml reaction flask equipped with mechanical stirrer, immersion thermometer, 150 ml addition funnel, water-cooled condenser, heating mantle and ice bath is placed 1.65 grams of sodium hydroxide pellets and 155 ml water. The resulting solution is warmed to 30°C. 75.6 35 grams (0.9 moles) of cyclohexanone is then added drop-wise with stirring while maintaining the temperature at 30-31°C. 43.0 grams (0.5 moles) of n-valeraldehyde

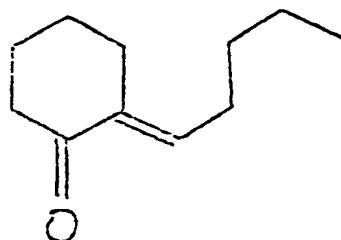
is then added dropwise with stirring over a period of about 30 minutes while maintaining the temperature at 30°C. The reaction mass is then stirred for 1 hour at 30°C. At this point, 3.0 grams of acetic acid and 100 ml 5 of water are added. The condenser is then replaced with a splash column and rush-over head and the reaction mass is heated to 95°C to distill the unreacted cyclohexanone. The reaction mass is then distilled until the head temperature is 100°C and the majority of the cyclohexanone 10 is removed. The reaction apparatus is then shut down and the reaction mass is cooled and poured into a separatory funnel.

The oil layer is taken up in diethyl ether and separated 15 from the aqueous layer. It is then washed with 1 volume of saturated sodium chloride solution and dried over anhydrous sodium sulfate and concentrated to yield 72.52 grams of crude product.

20

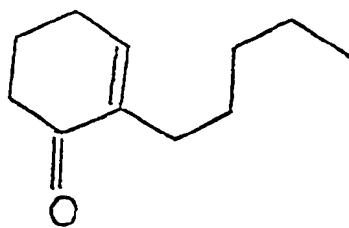
Example VI-BReaction:

10 into a 250 ml reaction flask equipped with mechanical stirrer, immersion thermometer, water-cooled condenser and heating mantel are charged 0.25 moles of the aldol condensation product produced according to Example VI-A  
5 and 138.6 ml of 5% hydrogen bromide in n-butanol (6.60 ml of 48% of HBr in 132 ml of n-butanol). The reaction mixture is heated to reflux (102°C) and maintained at reflux (monitoring by GLC) until all of the isomer having the structure:



is isomerized to the product having the structure:

20

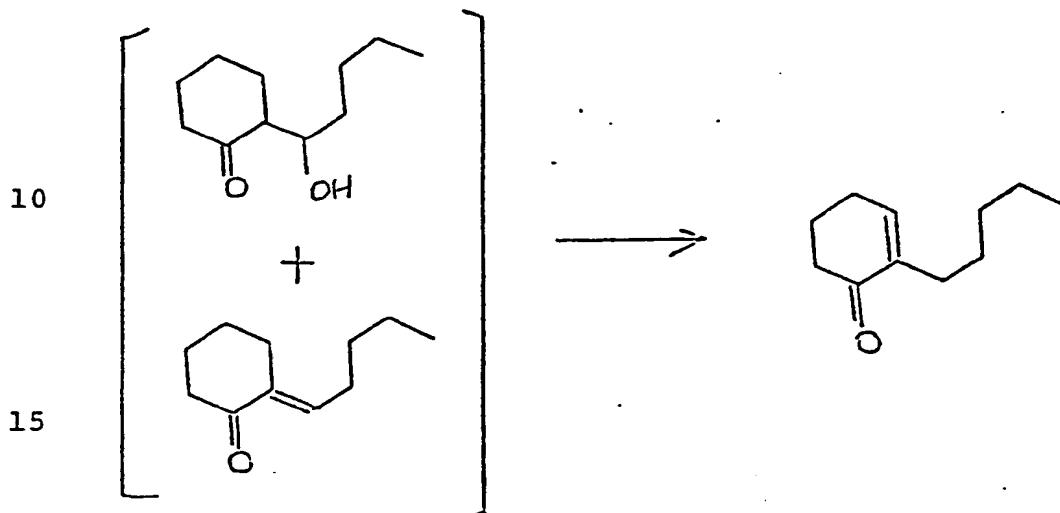


The ratio of endo:exo is about 14:1. The reaction  
30 apparatus is then shut down and the reaction mass is cooled and poured into a separatory funnel. The oil layer is then washed with 1 volume of saturated sodium chloride solution; followed by 1 volume of 10% sodium carbonate solution; followed by 3 volumes of saturated  
35 sodium chloride solution. The resulting material is then dried over anhydrous sodium sulfate and the crude material (172 grams) is distilled under vacuum. The

yield is 140 grams.

Example VI-C

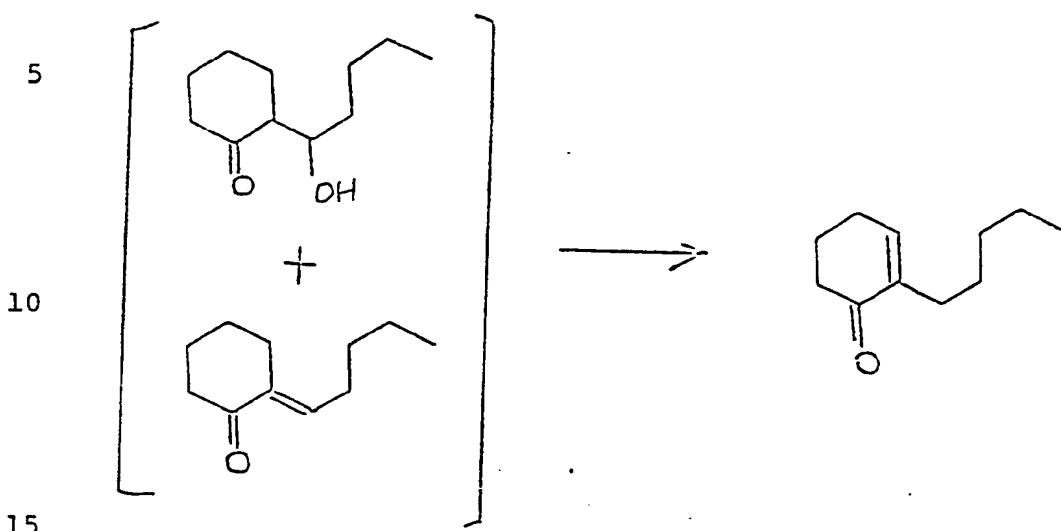
5 Reaction:



Into a 250 ml reaction flask equipped with mechanical  
20 stirrer, immersion thermometer, water-cooled condenser  
and heating mantle is placed 0.23 moles of the aldol  
condensation product of cyclohexanone and n-valeraldehyde  
produced according to Example VI-A and 176.4 ml of 5%  
hydrogen chloride in n-butanol (8.4 ml of 38% HCl in  
25 168 ml n-butanol). The reaction mass is heated with  
stirring to reflux and refluxed until a ratio of endo:exo  
isomer is about 13:1 monitored on a 6' x 1/4" SE-30,  
glass packed GLC column. The time of reaction is 170  
minutes. At the end of the 170-minute period the reac-  
30 tion apparatus is shut down and the reaction mass is  
washed with 1 volume of saturated sodium chloride  
solution followed by 1 volume of 10% sodium carbonate  
solution and 3 volumes of saturated sodium chloride  
solution. The product is then dried over anhydrous  
35 sodium sulfate to yield 230 grams of crude. The crude  
material is distilled under vacuum using a rush-over  
head. The yield of product is 140 grams.

**Example VI-D**

### Attempted Reaction:



Into a 250 ml reaction flask equipped with mechanical stirrer, Dean-Stark trap with Freidrich's condenser, immersion thermometer and heating mantle is placed 20.0 grams of the cyclohexanone-n-valeraldehyde aldol condensation product produced according to Example VI-A; 100 ml toluene and 2.28 grams (0.02 moles) of paratoluene sulfonic acid. The reaction mass is heated to reflux (114°C) with stirring and approximately 2.6 ml water is azeotropically distilled from the reaction mass.

The reaction is carried on for about 140 minutes and then the apparatus is shut down overnight for a period of 12 hours. The reaction is then restarted and run for 120 minutes additional time. The reaction mass is monitored on a 6' x 1/4" SE-30 GLC column until sufficient conversion appears to take place (about 13:1 endo:exo). The apparatus is shut down and the reaction product is cooled to room temperature.

The reaction product is washed with 1 volume of saturated sodium chloride solution; 2 volumes of 5% sodium carbonate solution; and 2 volumes of saturated sodium chloride solution. The product is then dried over anhydrous

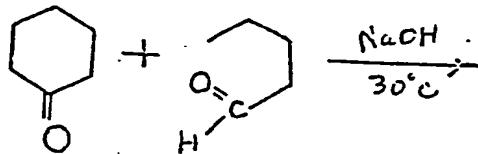
sodium sulfate and concentrated to yield 20.0 grams of crude material. The crude product is then rush-over distilled under vacuum yielding 11.1 grams of final product.

5

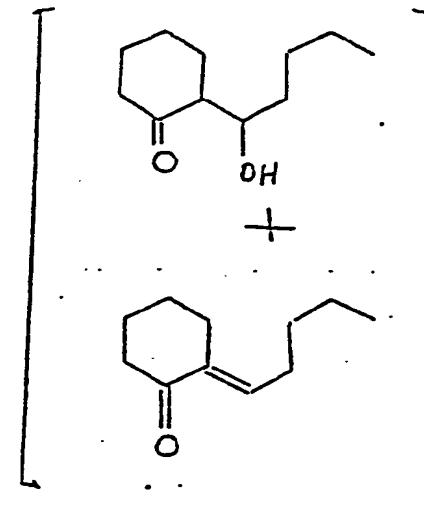
Example VIIReaction:

10

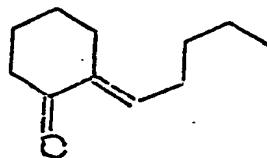
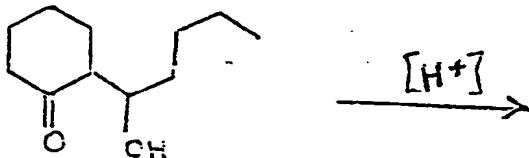
15



20

Reaction:

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30

Into a 5-liter reaction flask equipped with mechanical stirrer, 500 ml addition funnel, immersion thermometer, Friedrich's condenser, heating mantel and dry ice/isopropanol bath are placed 1.5 liter of water and 16.5 grams of sodium hydroxide. The resulting solution is warmed to  $30^\circ\text{C}$ . 9.0 moles of cyclohexanone is

added dropwise with stirring while maintaining the temperature at 30°C. After addition of the cyclohexanone, 430 grams (5.0 moles) of n-valeraldehyde is added dropwise with stirring keeping the temperature at 30°C  
5 using the isopropyl alcohol/dry ice bath as needed. The reaction mass is then stirred for a period of 1 hour at 30°C.

After 1 hour, 30.0 grams of acetic acid is added from a  
10 dropping pipette while maintaining the temperature at 30°C and stirring the reaction mass for 2-3 minutes thus obtaining in the reaction mass a pH of 6.

The reaction apparatus is then shut down and the reaction  
15 mass is poured into a separatory funnel where the water and oil layers are separated. The water layer is washed with 2 volumes of toluene and the toluene layer is combined with the oil layer and the washed aqueous layer is discarded. The organic layer is then washed  
20 with 2 volumes of saturated sodium chloride solution and filtered through cotton. The resulting organic material is then charged into a 5-liter reaction flask equipped with mechanical stirrer, Bidwell trap with bubble condenser, immersion thermometer and heating mantel and 10.0  
25 grams of oxalic acid is added to the reaction mass. The resulting mixture is heated to reflux with stirring and water is azeotropically distilled until no further water is evolved (about 9 hours). 95 ml water is recovered. The resulting mixture is then cooled to room temperature  
30 and poured into a separatory funnel. The organic layer is washed with 2 volumes of saturated sodium chloride solution followed by 1 volume of 5% sodium carbonate solution, followed by 2 volumes of saturated sodium chloride solution. The resulting organic material is  
35 dried over anhydrous sodium sulfate and concentrated to yield 485 grams of crude product. This material is distilled in vacuo using a 2" splash column and rush-

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over head. The yield of product is 375 grams.

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**25**

**30**

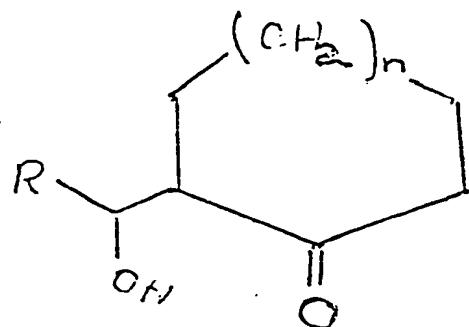
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## Claims:

1. The process of reacting a compound defined according to the structure:

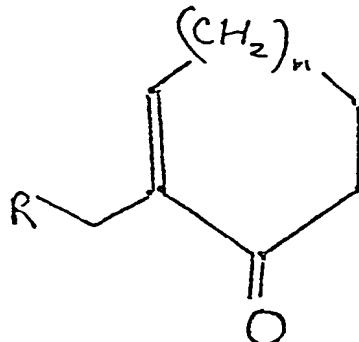
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with HX in the presence of n-butanol or toluene in order 15 to form, in one step, a compound having the structure:

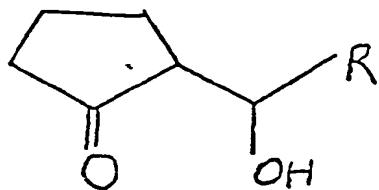
20



25 wherein n is 0 or 1, and wherein R is C<sub>1</sub>-C<sub>4</sub> alkyl and X is chloro or bromo.

2. The process of Claim 1 further characterized in  
that the process is a process of reacting the compound  
30 having the structure:

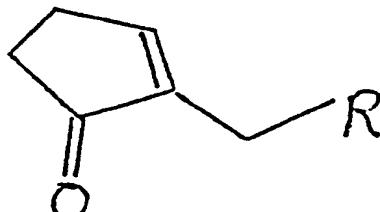
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with HX in the presence of n-butanol or toluene in order to form, in one step, a compound having the structure:

5

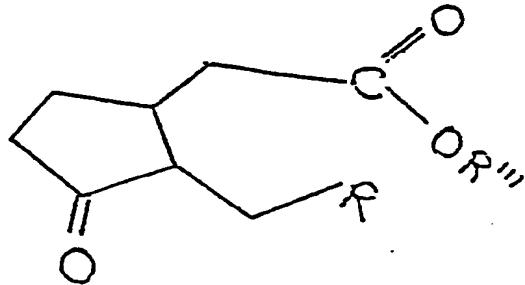


10

wherein R is C<sub>1</sub>-C<sub>4</sub> alkyl and X is chloro or bromo.

3. The process of Claim 1 further characterized in that  
15 it is a process for forming a compound having the  
structure:

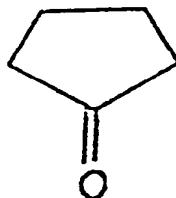
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comprising the steps of first reacting cyclopentanone having the structure:

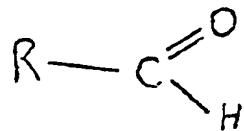
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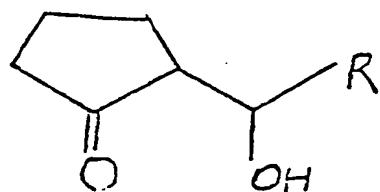
with an aldehyde having the structure:

5



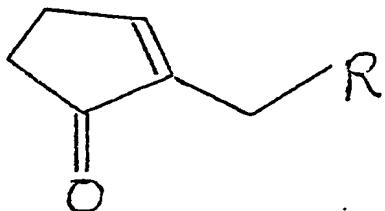
thereby forming an aldol condensate having the structure:

10



15 reacting the aldol condensate with HX in the presence of n-butanol or toluene thereby forming a compound having the structure:

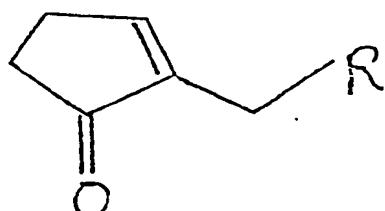
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reacting the compound having the structure:

30

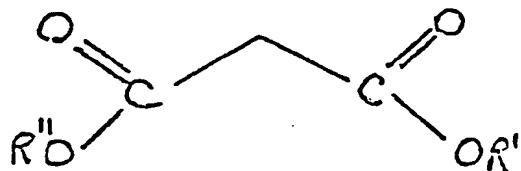


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with a malonic acid diester having the structure:

5

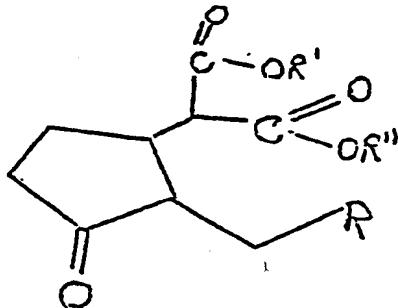


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thereby forming a malonic ester addition product having the structure:

15

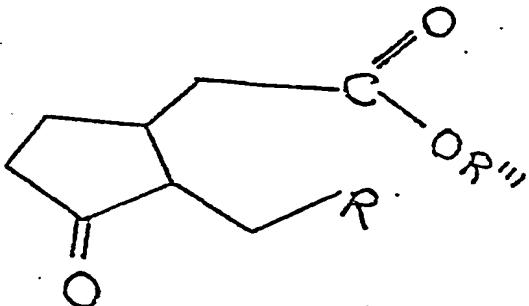
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reacting the malonic ester addition product with water at a temperature of about 200°C thereby forming a compound 25 having the structure:

30

35



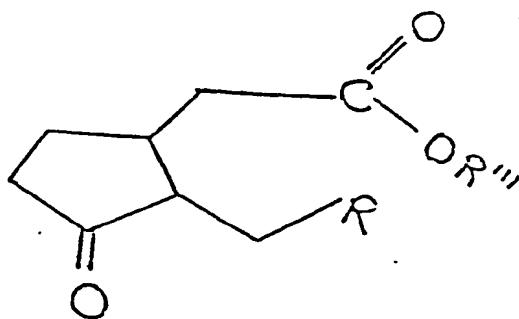
wherein R is C<sub>1</sub>-C<sub>4</sub> lower alkyl; R' and R'' are the same or different methyl or ethyl; R''' is ethyl or methyl and X is chloro or bromo.

5

4. The process of Claim 1 further characterized in that it is a process for forming a compound having the structure:

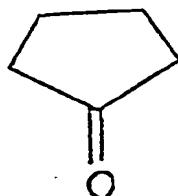
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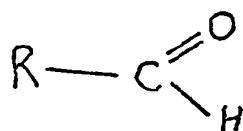
comprising the steps of (i) reacting cyclopentanone  
20 having the structure:

25



with an aldehyde having the structure:

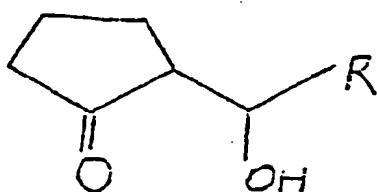
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thereby forming an aldol condensate having the structure:

5

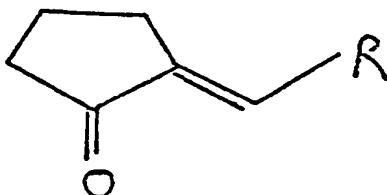


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(ii) reacting the thus-formed aldol condensate with an acid dehydrating agent, oxalic acid, thereby forming a compound having the structure:

15

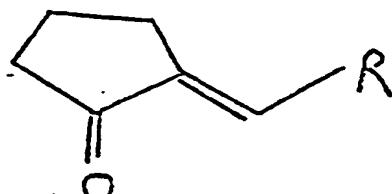
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rearranging the double bond in the compound having the structure:

25

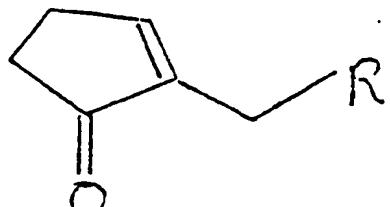
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with hydrogen bromide or hydrogen chloride thereby forming the compound having the structure:

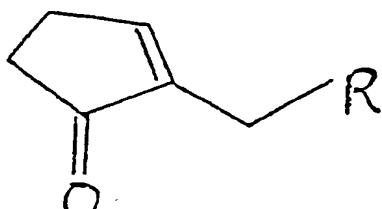
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reacting the compound having the structure:

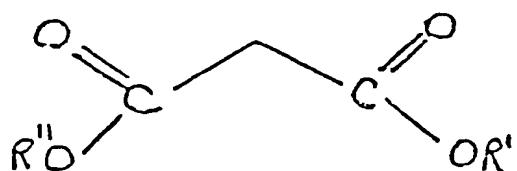
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with a malonic ester having the structure:

25



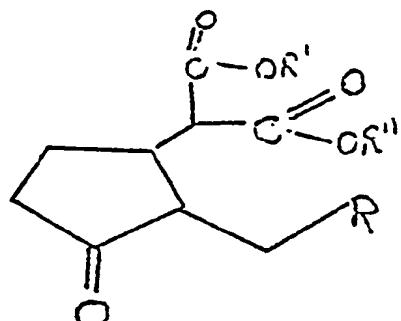
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thereby forming a compound having the structure:

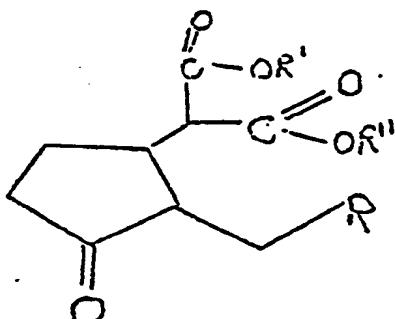
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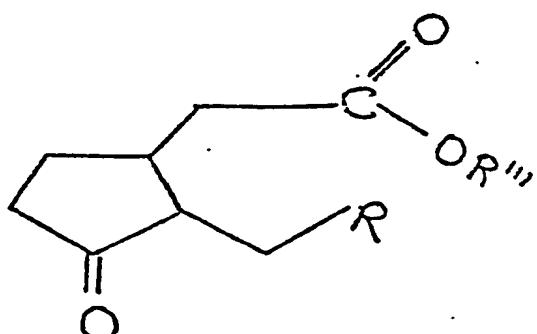
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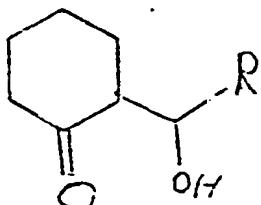


wherein R is C<sub>1</sub>-C<sub>4</sub> lower alkyl; R' and R'' are the same or different methyl or ethyl; R''' is ethyl or methyl and X is chloro or bromo.

5

5. The process of Claim 1 further characterized in that it encompasses a process of reacting the compound having the structure:

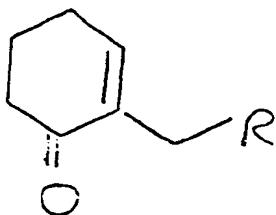
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with HX in the presence of n-butanol or toluene in order to form, in one step, a compound having the structure:

20



25

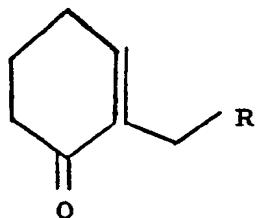
wherein R is C<sub>1</sub>-C<sub>4</sub> alkyl and X is chloro or bromo.

30

35

6. A compound having the structure

5



wherein R is C<sub>1</sub> - C<sub>4</sub> alkyl.

10 7. A process substantially as described according to  
any of Examples I-III or V-VII.

8. A compound whenever prepared by the process of any  
one of Examples I to V.

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FIG.1

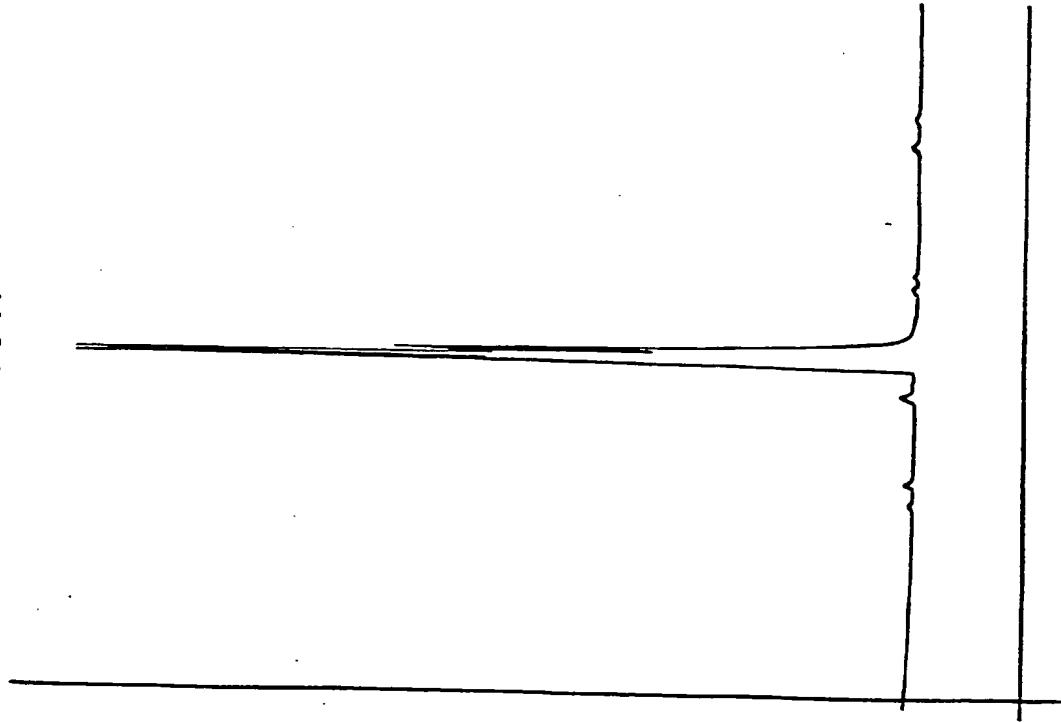
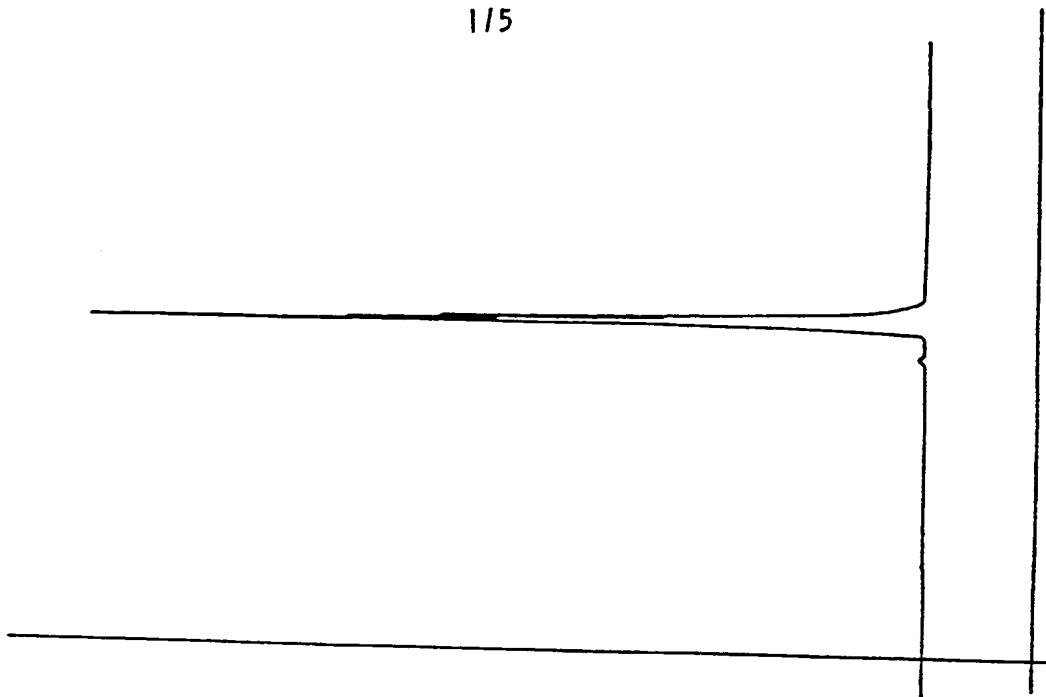


FIG.2



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FIG. 4

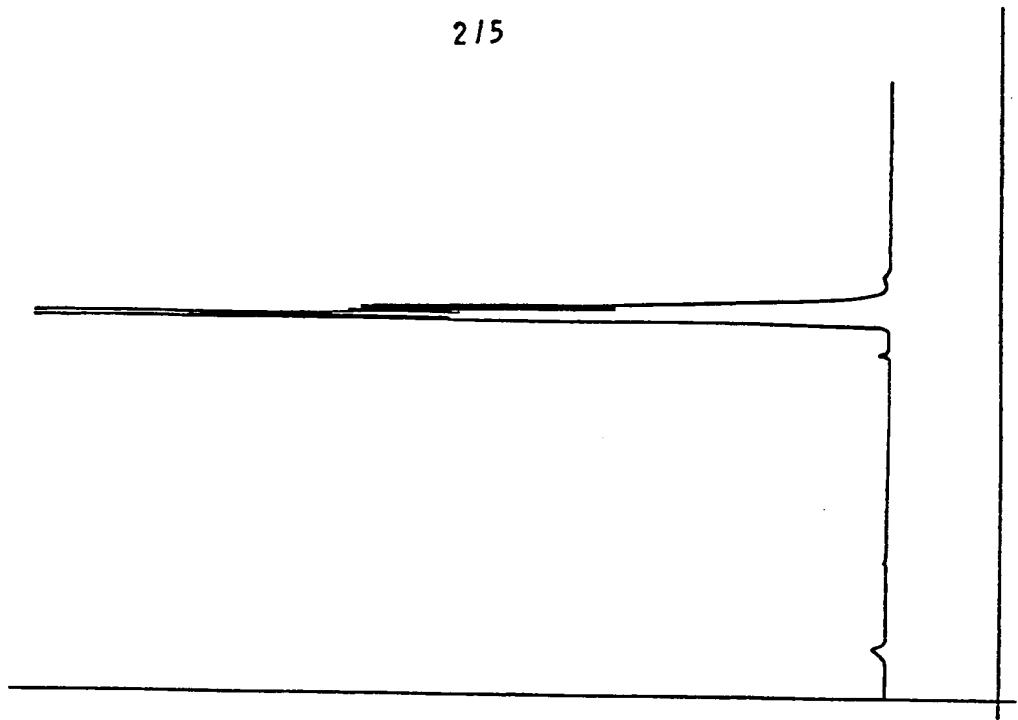
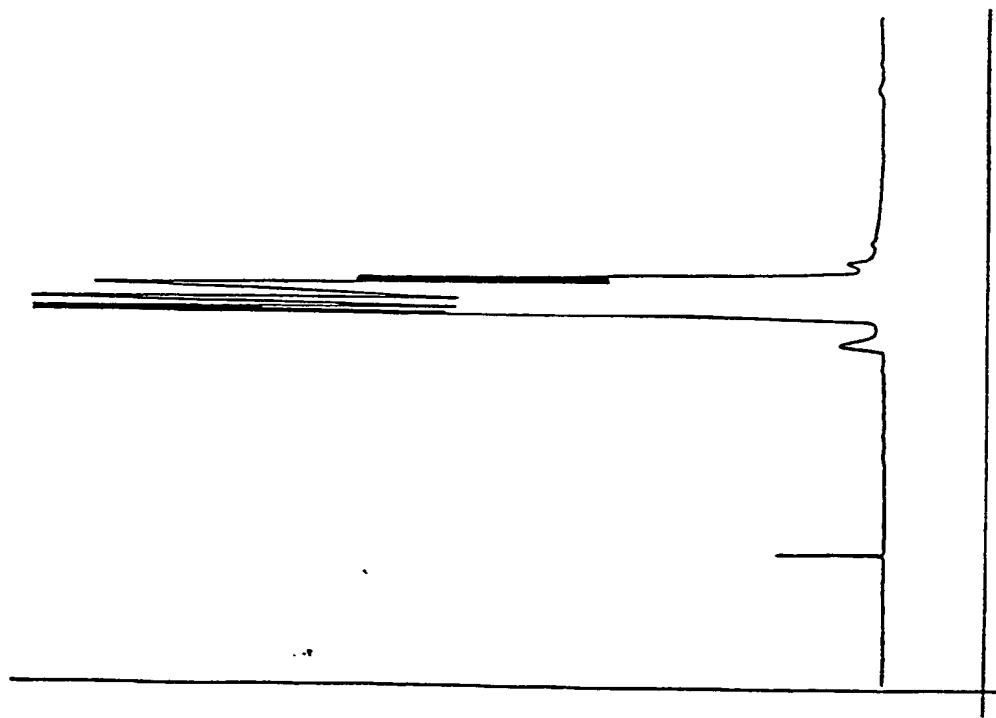


FIG. 3



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FIG. 6

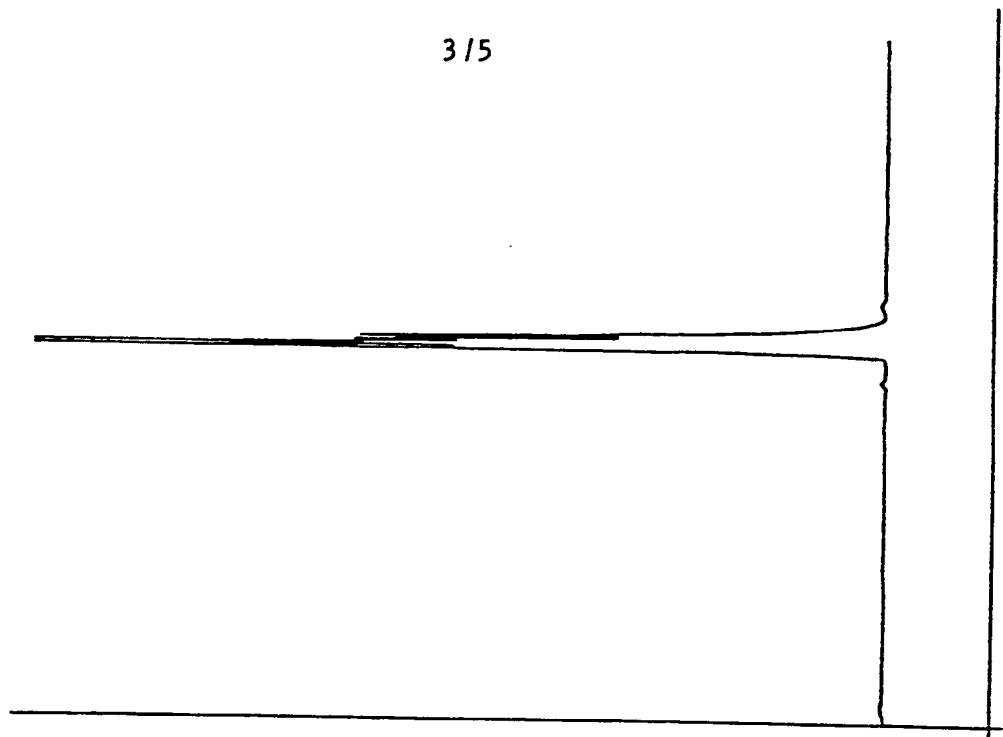
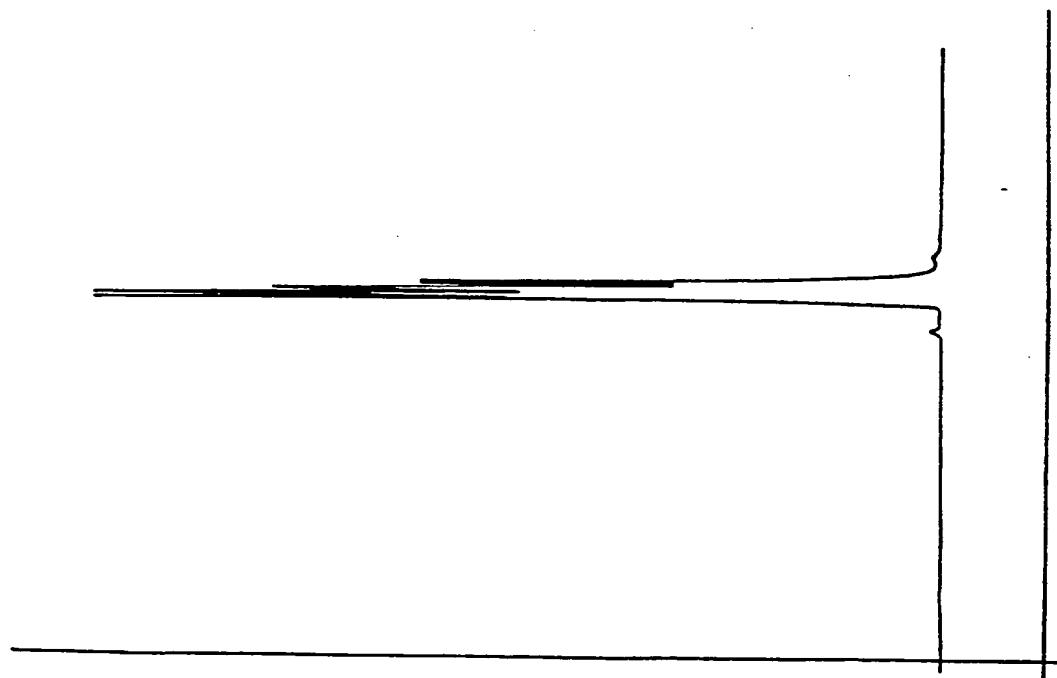


FIG. 5



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FIG. 8

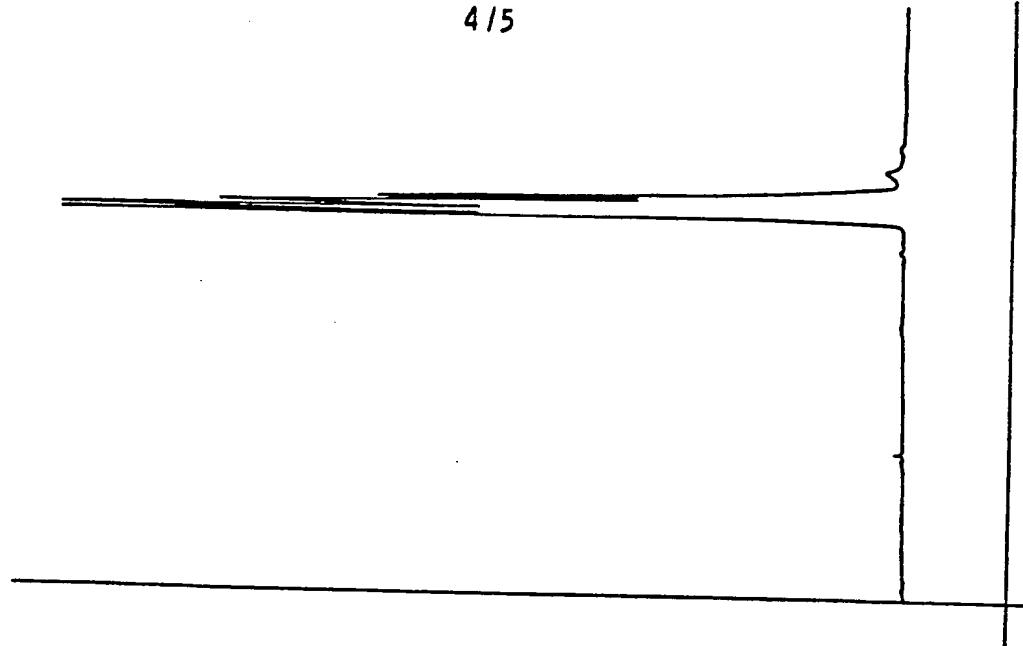
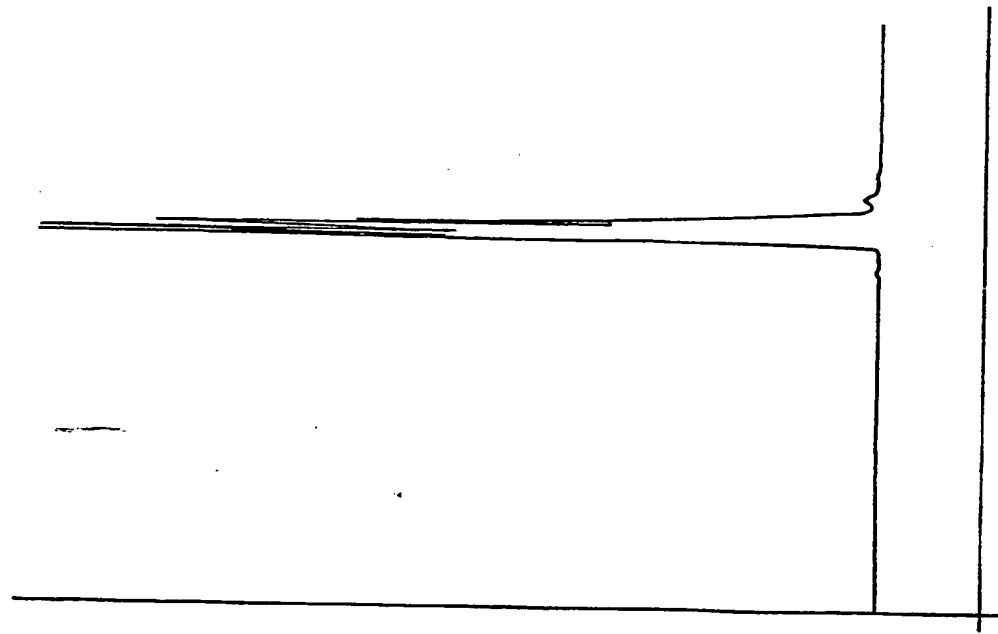


FIG. 7



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FIG.9

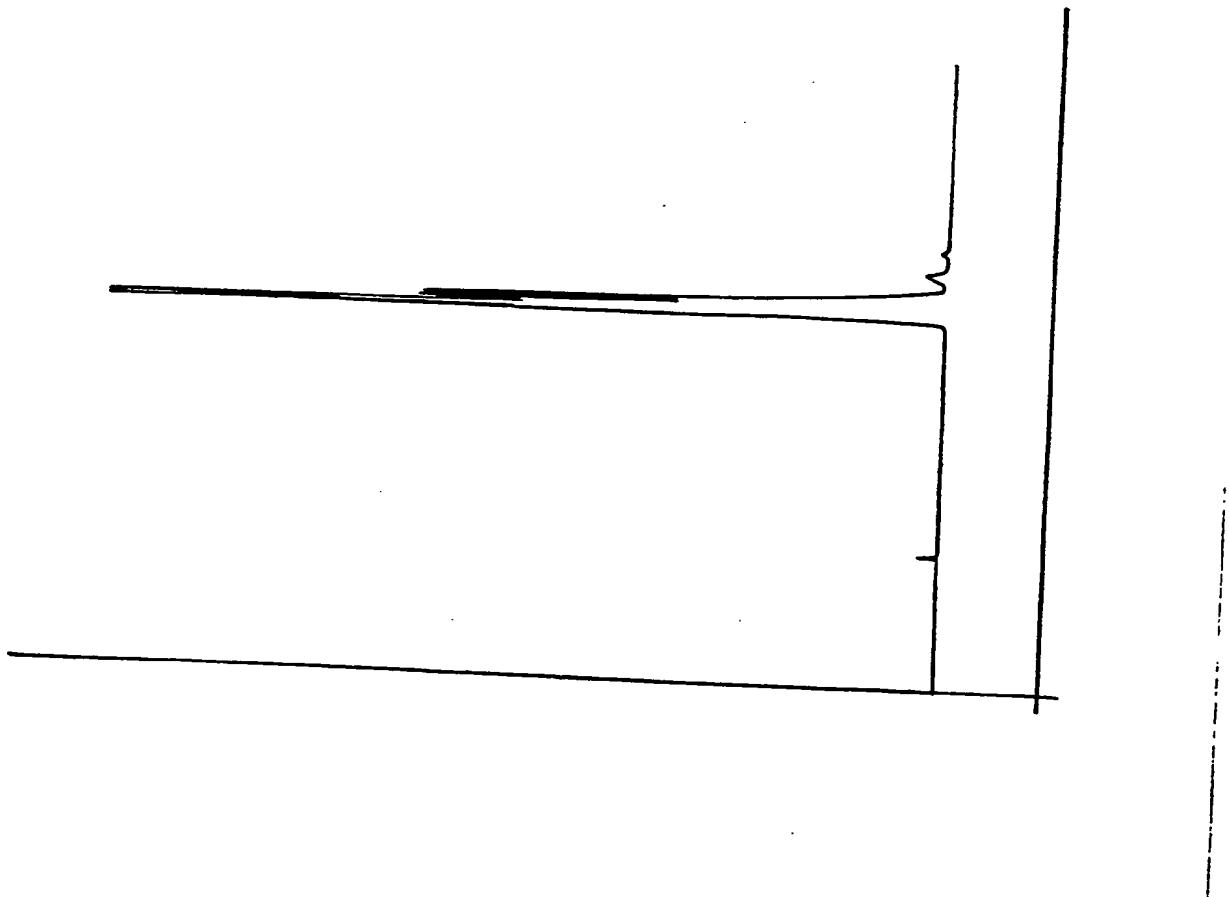
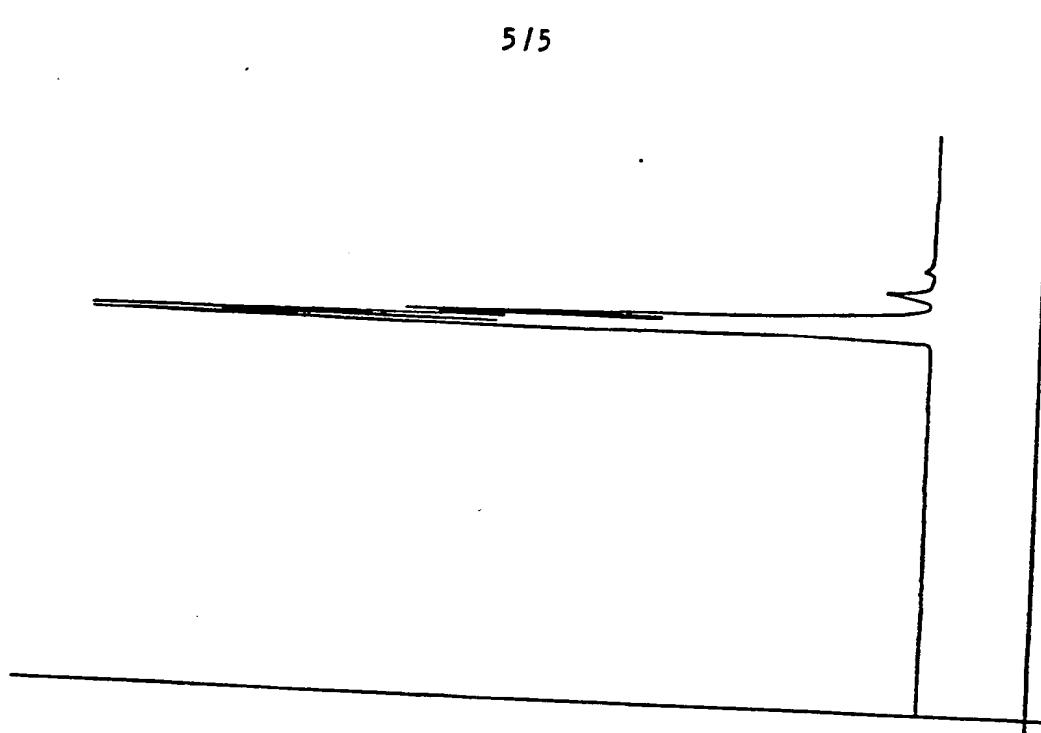


FIG.10



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0033604

European Patent  
Office

## EUROPEAN SEARCH REPORT

Application number

EP 81300207.8

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	<p><u>GB - A - 1 528 440</u> (SOCIETE ANONYME ROURE BERTRAND DUPONT) + Claims 1,2; example 1 + --</p> <p><u>GB - A - 1 347 667</u> (SOCIETE ANONYME DES ETABLISSEMENTS ROURE-BERTRAND) + Pages 1,2 + --</p> <p><u>US - A - 3 158 644</u> (EDOUARD DEMOLE) + Columns 1-3 + --</p> <p><u>DE - C - 956 948</u> (CHEMISCHE WERKE HÜLS) + Page 2, lines 13-58 + --</p> <p>CHEMICAL ABSTRACTS, vol. 75, 1971, Columbus, Ohio, USA POLAK'S FRUTAL WORKS N.V. "Alicyclic keto esters", page 405, abstract no. 109 953 n &amp; Neth. Appl. 69 18,228 -----</p>	3,4, 7,8  3,4  1,3,4, 6  3,4  3,4	C 07 C 49/527 C 07 C 45/66 C 07 C 69/716// A 61 K 7/46
			TECHNICAL FIELDS SEARCHED (Int. Cl.)
			C 07 C 49/00 C 07 C 69/00 C 07 C 45/00
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family. corresponding document
X	The present search report has been drawn up for all claims		
Place of search	Date of completion of the search	Examiner	
VIENNA	23-03-1981	REIF	